JUN 22 1920

VOLUME 25 NUMBER 6

ARCHIVES

OF

INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Boston — LOUIS V. HAMMAN, Baltimore

GEORGE DOCK, St. Louis — WARFIELD T. LONGCOPE, New York

W. S. THAYER, Baltimore

JUNE 15, 1920

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $6.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized on June 14, 1918.

CONTENTS OF PREVIOUS NUMBERS

JANUARY, 1920. NUMBER 1

Harmful Effects of Shallow Breathing with Special Reference to Pneumonia. Jonathan Meakins, M.D., Montreal.

Contributions to the Physiology of the Stomach. LII. Studies on Gastric Ulcer. A. C. Ivy, Ph.D., Chicago.

The Effect of Roentgen Rays on the Metabolism of Cancer Patients. Richard N. DeNiord, M.D.; Bernard F. Schreiner, M.D., and Hollis H. DeNiord, M.D., Buffalo.

The Cerebrospinal Fluid in Multiple Sclerosis. Joseph Earle Moore, M.D., Baltimore.

Cavity Formation and Annular Pleural Shadows in Pulmonary Tuberculosis. James A. Honeij, M.D., New Haven, Conn.

Rat Bite Fever. Report of a Case. Aaron Arkin, A.M., M.D., Ph.D., Morgantown, W. Va.

The Protein and Lipin Content of Blood Serum in the Nephritides. Max Kahn, M.D., Ph.D., New York.

FEBRUARY, 1920. NUMBER 2

A Study of the Colloidal Gold Reaction and Its Clinical Interpretation. Margaret Warwick, M.D., and Charles E. Nixon, M.D., Minneapolis.

An Analysis of the Spread of the Excitation Wave in the Human Ventricle. George Fahr, M.D., Madison, Wis.

A Clinical Study of Yellow Fever. Observations Made in Guayaquil, Ecuador, in 1918. Charles A. Elliott, M.D., Chicago.

Pericarditis with Effusion. An Experimental Study. Charles Spencer Williamson, M.D., Chicago.

Book Reviews.

MARCH, 1920. NUMBER 3

Studies on Arthritis in the Army, Based on Four Hundred Cases. I. Preamble and Statistical Analysis. Ralph Pemberton, M.D., and J. W. Robertson, M.D., Philadelphia.

II. Observations on the Basal Metabolism. Ralph Pemberton, M.D., Philadelphia, and Edna H. Tompkins, Boston.

III. Studies on the Nitrogen, Urea, Carbon Dioxid Combining Power, Calcium, Total Fat and Cholesterol of the Fasting Blood, Renal Function, Blood Sugar and Sugar Tolerance. Ralph Pemberton, M.D., Philadelphia, and Goodwin L. Foster, San Francisco.

A Method of Analyzing the Electrocardiogram. Hubert Mann, M.D., New York.

Irritation of the Vagus and Hemorrhagic Erosions of the Stomach. Knud Nicolaysen, M.D.

Clinical Studies on the Respiration. VI. A Comparison of Various Normal Standards for the Normal Vital Capacity of the Lungs. Howard F. West, M.D., Boston.

Experimental Determination of the Influence of Abnormal Cardiac Rhythms on the Mechanical Efficiency of the Heart. J. A. E. Eyster, M.D., and Edith C. Swarthout, M.D., Madison, Wis.

On the Platelet Count and Bleeding Time in Disease of the Blood. H. C. Gram, Copenhagen.

Book Review.

APRIL, 1920. NUMBER 4

Studies on Arthritis in the Army Based on Four Hundred Cases. IV. Studies in the Relation of Creatin Metabolism to Arthritis. Ralph Pemberton, M.D., Philadelphia, and Thomas E. Buckman, M.D., Boston.

V. Roentgen-Ray Evidences, Clinical Considerations, Treatment, Summary, Conclusions and Clinical Abstracts of Cases Studied. Ralph Pemberton, M.D., Philadelphia.

A Research on Blood Sugar in Depancreatised Dogs. B. J. Delatour, M.D., New York.

The Prognostic Value of Cholesterinemia in Chronic Nephritis: Final Report. Edwin Hences, Jr., M.D., Milwaukee.

Clinical Observations on Uuusual Mechanisms of the Auricular Pacemaker. Paul D. White, M.D., Boston.

Fetid Spirillar Bronchitis and Pulmonary Gangrene. P. Nolf, M.D., Liége, Belgium.

Book Review.

MAY, 1920. NUMBER 5

Experimental Pellagra in White Male Convicts. Joseph Goldberger, M.D., and G. A. Wheeler, M.D., Washington, D. C.

Experimental Pulmonary Edema. Benjamin H. Schlomovitz, M.D., Madison, Wis.

An Investigation of the Size of the Heart in Soldiers by the Teleroentgen Method. Alfred E. Cohn, M.D., New York.

Teleroentgen Measurements of the Hearts of Normal Soldiers. Bertnard Smith, M.D., Los Angeles.

Teleroentgen Estimations of Heart Size in Cases of Effort Syndrome. Bertnard Smith, M.D., Los Angeles.

Purulent Typhoid Meningitis: Report of a Case. E. A. Baumgartner, M.D., and H. H. Olsen, M.D., Halstead, Kan.

Observations on Changes in Form of the Initial Ventricular Complex in Isolated Derivations of the Human Electrocardiogram. F. A. Willius, M.D., Rochester, Minn.

The Influence of the Exposure of the Roentgen Ray on the Progress of Tuberculosis. Joseph A. Weinberg, M.D., Omaha.

Book Review.

COPYRIGHT, 1920, BY THE AMERICAN MEDICAL ASSOCIATION

Archives of Internal Medicine

VOL. 25 JUNE, 1920 No. 6

SODIUM CARBONATE IN CHLOROFORM POISONING*

EVARTS A. GRAHAM, M.D.
ST. LOUIS

In 1915 [1] I described some experiments which indicated that chloroform is dissociated in the body in such a way that free hydrochloric acid is formed from it and that the toxic effects of chloroform are probably to a great extent due to the action of the liberated hydrochloric acid. The evidence on which this view was based was as follows: 1. The ease of the formation of three molecules of hydrochloric acid from one molecule of chloroform outside the body by oxidation in the presence of water suggests that also within the body in the presence of water and available oxygen the same reaction might take place. 2. Lesions in the liver similar to those which occur in chloroform poisoning can be produced experimentally with hydrochloric acid. 3. Free hydrogen and free chlorin ions were demonstrable in the necrotic areas of the liver. 4. Observations on other chlorin substitution products of methane (dichlormethane and tetrachlormethane) showed that not only did they both have the property of producing central necrosis of the liver, but that also this property was in direct proportion to the amount of hydrochloric acid which each could yield theoretically in its breakdown, i. e., that the series ran in this order, $CH_2Cl_2 < CHCl_3 < CCl_4$ in respect to the power of each to produce central necrosis of the liver. 5. Other alkyl halides of the same type as chloroform, viz., bromoform ($CHBr_3$) and iodoform (CHI_3), produce lesions in the liver and elsewhere identical to those of chloroform; and evidence was submitted that at least in the case of iodoform the analogous halogen acid (hydriodic) is formed in the body, as shown by the fact that neutral salts of this acid are excreted in the urine. 6. The property of producing central necrosis of the liver is apparently one which is common to alkyl halides in general, since ethyl chlorid, ethyl bromid, ethyl iodid and ethylene bromid all produce the lesions seen in typical chloroform poisoning; and, furthermore, that ethyl bromid and ethyl

* From the Department of Surgery, Washington University School of Medicine.

1. Graham, E. A.: Late Poisoning with Chloroform and Other Alkyl Halides in Relationship to the Halogen Acids Formed by Their Chemical Dissociation, J. Exper. Med. **22**:48, 1915.

iodid are decomposed in such a way that hydrobromic and hydriodic acids, respectively, are formed in the body is indicated by the finding by other observers of inorganic bromin and iodin in the urine after inhalation of these substances. It was also found that the toxicity of these various substances was in direct agreement with their ease of dissociation outside the body. 7. That the property of producing liver necrosis was not dependent merely on the halogen content of the substance was shown by the fact that chloral hydrate ($CCl_3 - CH(OH)_2$), which like chloroform, has three chlorin atoms, produces relatively insignificant morphologic effects; and it is interesting that since this substance is excreted almost entirely as urochloralic acid, almost no hydrochloric acid could be formed from it within the body. 8. Sodium carbonate in hypertonic sodium chlorid solution partially inhibited the production of the lesions by chloroform. In one case it seemed to prevent the liver necrosis entirely; and uniformly its inhibitory effect on the usual swelling of the kidneys was very marked.

In a recent article by Davis and Whipple [2] the statements were made, "We have attempted to repeat Graham's observations on the protective action of sodium carbonate given intravenously during chloroform anesthesia," and "these experiments indicate that Graham's claims are based on incomplete or inaccurate observations. Carefully controlled experiments show beyond a reasonable doubt that carbonates given intravenously or by mouth have no effect whatsoever on the injurious action of chloroform on the liver."

Davis and Whipple used a method of experimentation somewhat different from that used in my own work, in that they administered chloroform to their dogs, for a period of one and one-half hours after a fasting period of three days, and for one and one-quarter hours after a fasting period of four days, instead of administering it for four and one-half hours to previously unstarved animals, as I had done. These authors state that they have found "that liver injury is much more uniform after a preliminary starvation; this renders the animals more susceptible to injury, hence a shorter period of anesthesia is advisable." From this we may conclude that Davis and Whipple worked with animals more susceptible to chloroform than those that I used.

Six experiments were conducted by them in all. To four chloroform poisoned dogs was given sodium carbonate in a hypertonic sodium solution; one dog received only "normal saline" solution, and another had no injection of either saline or carbonate. In my experi-

2. Davis, N. C., and Whipple, G. H.: The Influence of Drugs and Chemical Agents on the Liver Necrosis of Chloroform Anesthesia, Paper II, Arch. Int. Med. **23**:636 (May) 1919.

ments, on the contrary, eight dogs and four guinea-pigs were used. To four of the dogs and to two of the guinea-pigs sodium carbonate was given in a hypertonic sodium chlorid solution, and to the remainder was given only physiologic sodium chlorid solution. The object of conducting the experiments in this way was to provide a control for each animal which received the carbonate solution. The animals were always run in pairs, that is, both of two dogs or two guinea-pigs, of approximately the same weights, were given chloroform simultaneously for the same period of time, and while one of a pair was given an injection of sodium carbonate in hypertonic sodium chlorid solution, the other animal was given an equivalent amount of physiologic sodium chlorid solution in proportion to its body weight so that each of the two animals received the same amount of fluid per kilo. After completing the administration of the anesthesia, both animals of a pair were put under identical conditions as to diet, etc., and both were sacrificed at the same time (two days after the experimennt). It was felt that this method would provide the best means of controlling the experiment because it afforded in each case a direct comparison of animals which had been subjected to identical conditions, with the single exception that one animal received sodium carbonate and the other did not.

In my experiments conducted in this manner it was found uniformly that the animals which received the alkali had less necrosis than their controls, and in one case no necrosis at all occurred. It was also noteworthy that the alkali animals seemed less toxic, and at autopsy other changes characteristic of chloroform poisoning, as well as the liver necrosis, were less conspicuous than in the control animals. In spite of the statement of Davis and Whipple that "carefully controlled experiments show beyond a reasonable doubt that carbonates given intravenously or by mouth have no effect whatsoever on the injurious action of chloroform on the liver," I must disagree with them for the following reasons:

In their work, only two dogs were used for control purposes. These control animals were both dogs which had been given toxic doses of chloroform only a short time before (twenty-five and eleven days, respectively). Thus, these two served both as experimental and as control animals. It should be stated in this connection, that Davis and Whipple, instead of sacrificing the animals at the end of two days, merely removed small pieces of their livers and allowed the animals to remain alive. They consider that complete regeneration of the chloroform poisoned liver may safely be assumed to have occurred in this period of time, basing their decision on earlier experimental results. They do not demonstrate that it actually was complete in these particular dogs, and it is on this supposition very largely that

they question the validity of my results. Moreover, of the two control dogs, one received sodium chlorid solution intravenously, whereas the other received nothing, so that there was only one control of the carbonate experiments in the manner in which I had tried carefully to control all of mine.

Again, it is to be remarked, in reading the protocols of the experiments of Davis and Whipple, that in one of the carbonate experiments a note is made that "one of the old incisions has a superficial discharging pocket," and in another one that the dog is "recovering from distemper." It has been a frequent observation that infections, like all other conditions which remove glycogen, increase the susceptibility of animals to the toxic effects of chloroform; and for that reason it would seem unfair to draw conclusions from these dogs. Furthermore, it is noteworthy that the diets after the administration of the chloroform were extremely varied; for example, of the carbonate dogs, two had a "fat diet," one had a "casein diet," and nothing is stated about the diet of the fourth dog. Of the two controls, one had a "lean meat diet," and no information is given about the diet of the other. Moreover, even considering their experiments as recorded in their protocols, it is to be remarked that half of the dogs which received carbonate showed, as a matter of fact, less necrosis than one of the two controls.

Davis and Whipple are apparently inclined to consider the liver necrosis as the only important change produced by chloroform poisoning, as they ask "why chloroform passes by all body tissues until it reaches the liver, where the hypothetical chemical reaction takes place with release of hydrochloric acid." My position, however, has always been that although the liver is, perhaps, the most conspicuously affected organ, it is by no means the only one. In fact, Whipple's earlier articles directly controvert the idea of a specific susceptibility of the liver, inasmuch as he has shown in his own experiments that other tissues are affected to a sufficient degree to show pathologic changes.[3] The fact, for example, that the kidneys and heart muscle are markedly affected is so well known and has been observed so frequently by others that it would seem unnecessary to call attention to it again. I do not agree, therefore, that the liver necrosis is the only important change produced by chloroform poisoning. But I still hold the opinion that, since the decomposition of chloroform into three molecules of hydrochloric acid is an oxidation process in the presence of water, it is not surprising, in the light of the theory that the liver should show most conspicuously the anatomic changes of chloroform poisoning, in view of the fact that the liver is an organ in which oxidation processes are very active, and perhaps more active than elsewhere in the body.

3. Whipple, G. H., and Sperry, J. A.: Chloroform Poisoning. Liver Necrosis and Repair, Bull. Johns Hopkins Hosp. **20**:278, 1909.

This fundamental difference in assumption regarding the specific susceptibility of the liver to chloroform is of the greatest importance because it was possible to show that not only did sodium carbonate in hypertonic saline solution inhibit the necrosis of the liver, but that it diminished also the swelling of the kidneys. For example, on page 61 of my article referred to[1] it is stated, under experiment 3, that although there was a difference of weight between the two dogs at the beginning of the experiment of only one-half kilo (the weights being 4.5 and 5 kg., respectively) the respective weights of the kidneys at the time the dogs were sacrificed were 43 gm. and 68 gm., a difference of 25 gm.; that is, the kidneys of the dog which received the carbonate weighed only 43 gm. as contrasted with 68 gm. for the control. Likewise, the kidneys of the control dog were swollen and gray in appearance in contrast to a practically normal appearance of the kidneys of the carbonate dog. Moreover, in experiment 4, although the carbonate dog weighed 0.2 kg. more than the control (2.7 kg. and 2.5 kg., respectively), the former's kidneys actually weighed 9 gm. less than those of the control when the dogs were sacrificed. MacNider has corroborated my findings of the protective action of sodium carbonate on the kidneys in experiments in which he produced chloroform intoxication of dogs which had been rendered nephropathic by uranium nitrate. He states:[4] "The protection of the kidney by the carbonate, which is shown by the kidney being functionally much more active during an anesthesia than the kidney of a control animal, and by the lack of fatty degeneration, acute swelling, and necrosis of the renal epithelium which is constantly seen in the unprotected kidneys, is probably dependent on two factors: the neutralization of organic acids formed prior to and during the anesthesia, and the neutralization of hydrochloric acid which Graham has shown to be liberated by chloroform during an anesthesia induced by this substance." The anesthetic substance which he used was Gréhant's mixture which depends chiefly on chloroform for its anesthetic properties. Again, in a more recent article, he concludes as follows:[5] "A solution of sodium carbonate equimolecular with a 0.9 per cent. solution of sodium chlorid when given intravenously to anesthetized naturally nephropathic animals confers a variable degree of protection to the kidney."

---

4. MacNider, William de B.: The Inhibition of the Toxicity of Uranium Nitrate by Sodium Carbonate, and the Protection of the Kidney Acutely Nephropathic from Uranium from the Toxic Action of an Anesthetic by Sodium Carbonate, J. Exper. Med. **23**:171, 1916.

5. MacNider, William de B.: The Stability of the Acid-Base Equilibrium of the Blood in Naturally Nephropathic Animals and the Effect on Renal Function of Changes in This Equilibrium. II. A Study of the Efficiency of an Alkali to Protect the Naturally Nephropathic Kidney Against the Toxic Effect of an Anesthetic, J. Exper. Med. **28**:517, 1918.

Davis and Whipple state also, that in my work "it was found that central liver necrosis followed the use of: (1) dichlor- and tetrachlormethane (in proportion to chlorin content)." Particular pains were taken in my article to state that the chlorin (or halogen) content of the molecule had nothing whatever to do with the production of the lesions, but that rather it was the production of the respective halogen acid from the molecule which was important. On page 68 of my article, the statement is made, "These results seem to afford striking confirmation of the idea that the essential factor in the production of these severe lesions by alkyl halides is the halogen acid formed by decomposition rather than merely the halogen content of the molecule," and again on pages 68 and 69, "Moreover, that the mere presence of halogen atoms in the molecule is not the responsible factor is demonstrated by the fact that chloral hydrate ($CCl_3-CH\begin{matrix}/OH\\ \backslash OH\end{matrix}$), which, like chloroform ($CHCl_3$), possesses three chlorin atoms, produces relatively insignificant morphologic effects. Some other factor must therefore be responsible. Evidence has been submitted to show that an important factor is probably the halogen acid (hydrochloric, hydrobromic, or hydriodic acid) which is formed by chemical dissociation of the alkyl halides within the body. That these substances form their respective halogen acids in the body is shown by the occurrence in large quantity of the neutral salts of these acids in the urine. In this respect they differ from chloral hydrate, which is excreted mainly as urochloralic acid, and of which therefore only a small portion is decomposed to give neutral chlorides."

Again Davis and Whipple state (p. 649), "In an article published in 1912, Graham makes the statement that chloroform is one of a group whose effect on organs is like that of asphyxiation. He has later amplified this statement with the suggestion that many common anesthetic substances, including chloroform and ether, also carbon monoxid and potassium cyanid, are capable of dissociating in a manner which yields bivalent or unsaturated carbon. It is easy to imagine that such compounds might then appropriate oxygen within the body, in order to satisfy their free bonds." It was natural to think of the possibility of the direct union of bivalent carbon with oxygen at the time my article in question was in preparation. But the idea was dismissed because there is little or no evidence to support it, at least as regards a group reaction. In fact, Bürker,[6] as early as 1910, suggested the possibility that the suppression of oxidations during narcosis is due to the appropriation of oxygen by the anesthetic substance. This

6. Bürker: Eine Neue Theorie der Narkose, München. med. Wchnschr. **57**:1443, 1910.

whole question, of course, involves a consideration of many factors of which one is a difference in oxidation potential between the narcotic substance and the countless other substances in the cell which are oxidizable. As Verworn [7] has pointed out, in so far as narcotic substances as a class are concerned, carbon dioxid offers one serious difficulty to such a belief because of its inability to be further oxidized.

It is not to be expected that absolute inhibition of chloroform liver necrosis can uniformly be obtained by the use of such an alkali as sodium carbonate, for the reason that this substance gains entrance to the cell with difficulty. On page 59 of my article the statement is made: "The degree of inhibition of the necrosis was subject to wide variations in the different experiments." Also on the same page attention was called to the fact that only once was complete inhibition obtained. This fact serves to emphasize all the more strongly the need of controlling the alkali experiments carefully. In this connection the recent excellent work of Lynch, Smith and Marshall,[8] on "mustard gas" poisoning is of very great interest. For they also come to the conclusion that the chief toxic effects of mustard gas are to be ascribed to the hydrochloric acid liberated from the mustard gas within the body. Also, as in my own work, these authors found that an inorganic alkali (sodium bicarbonate), partially inhibited the toxic effect but not to uniform degree in all their experiments.

Because, however, Davis and Whipple disagree with my former results with sodium carbonate, it seemed desirable to perform another experiment. Two normal adult dogs were placed in adjacent cages for three days preceding the experiment and were given a liberal allowance of meat, bread and water. They were then given chloroform (Mallinckrodt's "Purified for Anesthesia") for four hours, by inhalation, and kept as nearly as possible at the same depth of narcosis. Immediately before the anesthesia Dog A weighed 7,240 gm. and Dog B weighed 5,675 gm. During the anesthesia Dog A received 239 c.c. of Fischer's hypertonic sodium carbonate solution (Na_2CO_3, 10, H_2O, 10 gm.; NaCl, 14 gm.; distilled water, 1,000 c.c.), which was the same solution and the same proportionate amount as used in my earlier work. To Dog B was given an equivalent amount (187 c.c.) of sterile physiologic sodium chlorid solution (0.85 per cent. NaCl). In both instances the solutions were warmed to body temperature and injected slowly into the external saphenous vein. After being returned to their cages, both dogs were allowed meat, bread and water freely. On the following day Dog A (alkali) was found to be lively and responsive,

7. Verworn: Irritability, Yale University Press, 1913, p. 260.

8. Lynch, V., Smith, H. W., and Marshall, E. K.: On Dichlorethylsulphid (Mustard Gas). I. The Systemic Effects and Mechanism of Action, J. Pharmacol. & Exper. Therap. **12**:265, 1918.

but Dog B (control) lay curled up in his cage. Dog B had vomited several times, but no vomited material was seen in Dog A's cage. Dog B died twenty hours after the completion of the administration of the chloroform.

Four hours later (twenty-four hours after terminating the chloroform administration) Dog A was killed with chloroform, and both animals were immediately examined at necropsy. While being given the chloroform to kill it Dog A (alkali) was sufficiently active to struggle vigorously. Very marked gross differences were found in the appearances of the organs. The liver of Dog B (control) was very edematous and yellowish cream colored, as if it contained an enormous amount of fat. On the other hand, Dog A's liver was purplish red in color and contained apparently only a moderate amount of excess fat. Also, the kidneys of Dog B were gray in color and were clearly more swollen than those of Dog A. The comparative weights of the organs were very interesting. Although Dog B (control) weighed 1,600 gm. less than Dog A (alkali), its liver weighed 6 gm. more (270 gm. and 264 gm., respectively) than that of Dog A, and its kidneys weighed 5 gm. more (43 gm. and 38 gm., respectively).

The greater weight of Dog B's organs was interpreted as being due probably chiefly to increased edema. To determine this point more accurately, however, a portion of the liver of each dog was evaporated to dryness on a steam bath, and the water content of both A's and B's livers was found to be 73.6 per cent. and 79.5 per cent., respectively. In other words, therefore, the liver of the control dog had a water content 6 per cent. greater than that of the dog which received alkali. Microscopically, also, there was a marked difference in the amount of necrosis in the two livers. In Dog B the necrosis was practically complete throughout the whole section with scarcely any parenchymatous cell which seemed even fairly normal. In Dog A (alkali), on the contrary, although the necrosis was marked, it varied in amount in different lobules from an involvement of from three-fourths to four-fifths of the lobule. At the periphery of each lobule there was a border of several rows of parenchymatous cells which were practically normal, except for some fat vacuoles. Dr. Opie very kindly examined the livers of both dogs for me, both in the gross and from the microscopical slides, and he has permitted me to state for him that the difference in the amount of necrosis in the two livers was so striking as to be unquestionable. This experiment, therefore, is confirmatory of my earlier work, and it shows that dogs may be protected to a variable extent from the effects of late chloroform poisoning by the administration of sodium carbonate.

Finally, it should be said that the failure to obtain complete inhibition nor even uniformly striking inhibition of chloroform necrosis of the liver by alkali, does not constitute a serious objection to the idea that the toxic effects of the alkyl halides are due largely to the action of halogen acids liberated from the respective substances. The large amount of other evidence for the idea which is summarized in the opening paragraph of this article cannot be controverted by the mere fact that sodium carbonate will not always completely inhibit chloroform necrosis of the liver.

A STUDY OF MULTIPLE CARTILAGINOUS EXOSTOSIS

FOUR CASES WITH REPORT OF CALCIUM AND MAGNESIUM METABOLISM IN TWO CASES

JAMES A. HONEIJ, M.D.
NEW HAVEN, CONN.

The first case was seen by me in 1912 in the service of Dr. Francis H. Williams at the Boston City Hospital, since which time several cases have been studied. Early in 1917 a case in New Haven came under observation and was referred to me by Dr. William F. Verdi. It was studied essentially for calcium and magnesium balances in conjunction with Drs. Frank P. Underhill and Jean L. Bogert. Eighteen months later a second case was studied, and the results compared with those found in the first case. During this time, two other cases were under observation but no study of the calcium and magnesium metabolism was made.

This report covers the complete examination of four cases, from a clinical, osteologic and roentgenographic point of view and includes the metabolic results in two of them. A pathologic report of a growth removed in one case is also attached.

A brief review of the literature is given here and an analysis showing the bones affected in sixty-six cases, as well as other information bearing on the questions brought out by this investigation.

REPORT OF CASES

Case 1.—R. B., American, born in Connecticut, aged 22, male; single; occupation, clerk. Outpatient. March 7, 1918.

Diagnosis.—Multiple exostosis.

Complaint.—None, except pain off and on up until two years ago.

Past History.—Patient is one of six children: three brothers and two sisters. Weight at birth, 7 pounds; normal delivery; breast fed. Had chicken pox, measles and whooping cough as a child.

Present History.—At birth, feet were flexed upward against lower legs. These gradually came down and patient was able to walk normally at 1 year of age. Slight impediment of speech was noticed in early life. He lisped, pronouncing "c" and "s" as "th." At 2½ years of age he was taken sick during the summer and had chills every day, followed by fever and aching feeling. These chills did not occur at regular hours each day—thought to be malaria. When 7 years old (listless and did not play) a doctor was called who examined him, finding his knees, ankles, legs and wrists swollen and prominent but not painful. Was given lime treatment and nourishing foods. He improved rapidly. From then up to his tenth year he had whooping cough, measles and chicken pox. Since then he has had no disease. As a young boy, he played the usual games, but noticed that his limbs ached on rainy days. Photographs at 2½ and 7 years of age show a distinct asymmetry of face. There is also a slight deviation of the hands so that the radial styloid process is prominent.

Patient has no complaint, except that he tires easily on working much. Appetite normal. When examined for the draft his weight was 100 pounds stripped. At present date he weighs 111 pounds without coat and vest.

Physical Appearance. — Rather poorly developed and undersized individual. Narrow and slightly built with rather prominent bones. Is knock-kneed, his left leg being especially curved; flat-foot; ankles are prominent. It is noticed that his forearms and lower legs are much shorter in proportion to the rest of his body (Fig. 1). Hips are narrowed. Chest is flattened and the ribs are quite prominent. Distinct bone protuberances on upper bones, especially anterior surface right thigh. Hands are short and there is marked disproportion in length of fingers. Face is distinctly asymmetrical. Distinct bony protuberances are felt around upper arm and lower thigh (Fig. 2), also marked irregularity of the ribs. The wrists are enlarged and very irregular, as are also the knees and ankles. Motion of shoulders, wrists, knees and ankles is decidedly limited. There is nothing else of particular note.

Fig. 1.—Case 1, R. B. The forearms and lower legs are short in proportion to the remainder of the body. The hips are narrow; the ankles prominent; knock knees, especially the left.

Lung and heart examination is negative. Skin is normal, although rather dry. The examination of the mouth shows unusually high palate and there is a distinct deviation of the septum.

Roentgenographic Examination.—

Skull: (Not obtained.)

Vertebral Column: There is a lateral curvature and slight kyphosis. Vertebrae are not large and the upper five dorsal show a greater transparency than is usual. The first, second and third dorsals appear somewhat compressed.

Ribs: The thorax shows marked asymmetry (Fig. 3). The ribs show a most unusual increase in their downward angle or direction. This is especially true of the six upper ribs. The ribs themselves are bowed, the upper six, except the first, are considerably narrower than the others. Anterior processes are decreased and in some places are practically obliterated, the ribs overriding one another. There are no definite exostoses.

Fig. 2.—Case 1, R. B. Protuberance on anterior surface of right thigh.

Clavicles: Are considerably bowed, even in diameter throughout, heavy, show no exostoses.

Scapulae: Of normal proportions. The right is somewhat irregular in outline at its outer border. The acromion processes are rather large. Glenoid fossae are rather shallow, small, especially so when compared with the size of the heads of the humeri, especially the left.

Pelvis: Is small. Lower portions, including the os pubis and ischii, show a rotated development. All the bones appear poorly formed, irregular in shape and outline. There are definite outgrowths on the iliae and the os pubis is bowed and much increased in width. The symphysis pubis is somewhat increased in width. The sacro-iliac synchondrosis is extremely irregular in outline. The left acetabulum is irregular in outline and the right somewhat shallow. The density of the pelvic bones, especially the lower portions of the ilii, is somewhat increased. The pelvic cavity is asymmetrical.

Humeri: Right, approximately 31 cm. in length. Left, approximately 28 cm. long. Ends are very large and the neck on the left side is also much increased in width. The width of the head on the right is approximately 4.5 cm. and on the left approximately 5.5 cm. The shaft is approximately 3 cm. on the right and 2.7 cm. on the left. There are definite exostoses on the middle of the shaft on both sides, and on the left between the middle and the head, posterior surface. The bone is heavy and shows no transparency as has been evident in some of the other cases. The joint surfaces are apparently clear. Epiphyseal lines are barely discernible.

Radii and Ulnae: Extremely bowed, so much so that the radius crosses the ulna at its upper third (Fig. 4). Approximate length is 21 cm. on the right, 20.5 cm. on the left. The ulna is 21 cm. on the right and 23 cm. on the left. The articulation is very free between radius and ulna. Bones are somewhat increased in width and proportion. The lower ends of the radii show the greatest increase in width. The bone is affected for approximately 8 cm. on the left and practically the whole length on the right. There are

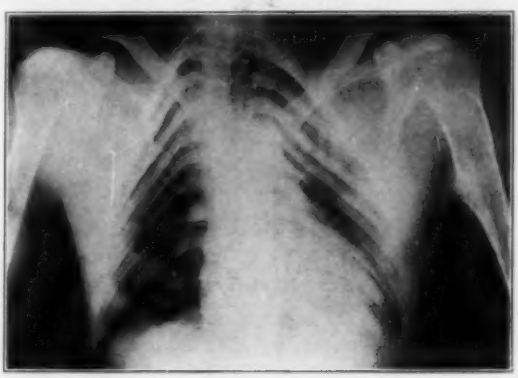


Fig. 3.—Case 1, R. B. Asymmetry of thorax; bowing of ribs; small scapulae and large humeri.

small exostoses. The ulna shows the same changes excepting the greatest increase in width is at its proximal head. The lower ends, however, are considerably deformed, are somewhat transparent and show exostoses. The styloid processes are not developed. The epiphyses are not determined. Joint spaces are clear.

Femora: The length of the femora is not determined. They are approximately from 53 to 56 cm. in length. The left femur is somewhat heavier and wider than the right. The right, however, shows the greatest deformity and the only definite cauliflower-like exostosis (Fig. 5). Greatest width, head of right femur, is approximately 8 cm. and the left 8.5 cm. Appearance of the ends is clublike, with irregular outline, enormously widened neck and although showing irregular growth, shows no definite exostoses. The exostosis on the right shows a definite outgrowth, continuous with the bone, is some 5 cm. in length by 3.5 cm. in width. There appears to be little cartilage and its density is even greater than that of the normal bone. Above this growth are two similar rounded, prominent processes, one of which appears as an outgrowth from

Fig. 4.—Case 1, R. B. Disproportion between radius and ulna; radius is curved; styloid process is rounded; exostoses; disproportion of carpal bone.

Fig. 5.—Case 1, R. B. Cauliflower exostosis on femur.

the cortex (Fig. 6). The lower ends of the condyles appear to be somewhat squared, surface slightly flattened, but otherwise within normal limits. The bones do not appear to be transparent but the longitudinal striations as normally seen are very irregular and also irregular in density. The epiphyses of the heads are clearly discernible. The condyles, however, are not seen.

Tibia and Fibula: The right tibia is 36.5 cm. in length and the fibula 34 cm. This is not the true length of the fibula as it apparently fuses with the tibia about 8 cm. above its lower end. At this point the tibia is 4.5 cm. in width, whereas, through the malleoli it measures only 6 cm. in width. The middle of the shaft is 2.5 cm. in width. The head is 8 cm. The head of the fibula is 3.5 cm. in width and just below the head the width is 3 cm. The

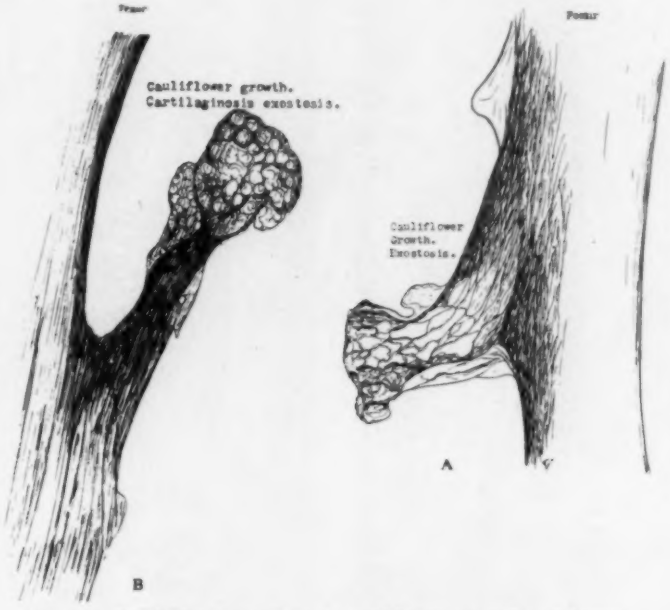


Fig. 6.—Cartilaginous exostoses, cauliflower growth, on femur.

middle of the shaft is 1 cm. and the lower end is 3 cm. The left tibia is 36.5 cm. and the fibula is 32 cm. in length. The fibula is fused to the tibia at its upper and lower extremities by a clublike formation which is approximately 6 cm. in length. The tibial head is 8 cm. wide, middle of shaft is 2.5 cm. and the lower end is approximately 5 cm.; with the fibula which is fused to it, it is approximately 7 cm. At the upper extremity where the fibula and tibia are fused the width is 7.5 cm. The fibula, middle of shaft, measures 1.5 cm. Width of the ends is not determined. Bones show very little transparency, rather heavy penciling and longitudinal lines. There are distinct growths as part of the bone, although on the right the fibula just below the head shows an exostosis which apparently arises from the cortex which shows as a heavy opaque line, about 2 cm. in width. Bones are slightly bowed,

except the left fibula. The epiphyseal lines are not determined. Joint space is clear. Tibial heads are not massive but show some surface flattening (Fig. 7).

Lateral view of right tibia, 8 cm. from lower end, shows a very marked boblike exostosis which has pushed into the fibula, has bent it backward and has directly interfered with its growth. It is this point which appears as a fusion on the anteroposterior view. The lower end of the fibula, however, is distinctly fused with the tibia (Fig. 8).

Hands: Carpals: The os magnum is enormously developed as compared with the other bones. All the bones are somewhat irregular in shape.

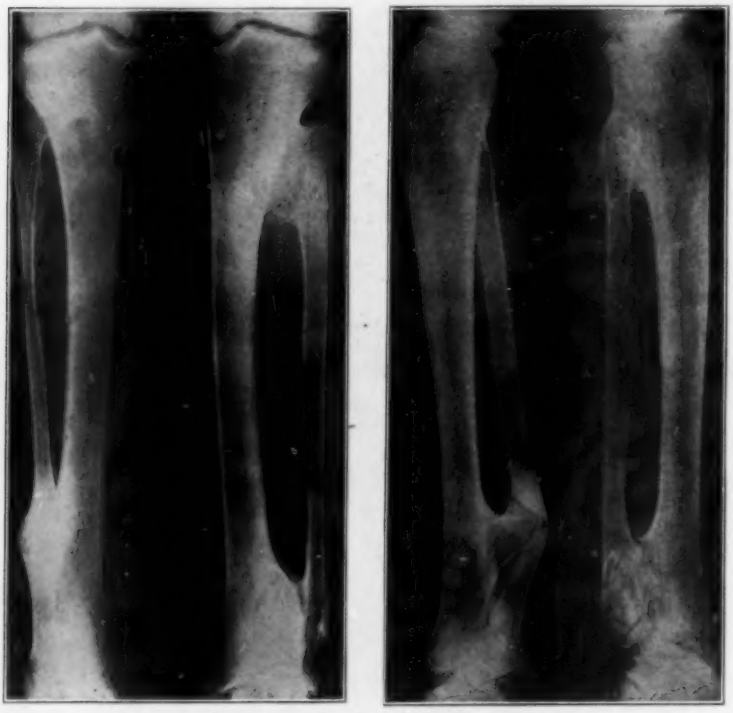


Fig. 7.—Case 1, R. B. Anteroposterior and lateral views of tibiae and fibulae.

Metacarpals: Show the usual disproportion in length. The longest bone of the right hand is the second metacarpal which is 6.2 cm. long. The first is the shortest. It measures 4 cm.; the third, 5.7 cm.; the fourth, 5.8 cm., and the fifth, 5 cm. The ends of the bones are somewhat increased in width, especially the second metacarpal. The changes, however, are slight, as compared with the other bones. The longest bone of the left hand is the second which measures 6.5 cm., the shortest is the first, which measures 4.2 cm. The third measures 6.3 cm.; the fourth measures 5.5 cm. and the fifth 5.4 cm. The third metacarpal shows some increase in width throughout and the second and fourth show small exostoses.

Phalanges: A few of the bones show some increase in width, are irregular in form and show small exostoses. Penciling is very distinct. There is also disproportion in length. Joint spaces are clear. The epiphysis is not determined in any of the bones, either phalanges or metacarpals.

Feet: The length of the metatarsal bones is increased and they are disproportionate in length. They show a few small exostoses; changes are not marked. Phalanges also show deformities, change in shape, size and length, with exostoses on several. Some penciling of the bone is seen. Joint surfaces are clear. Epiphyseal lines are not determined.

CASE 2.—E. D., female, Italian (born in the United States), aged 16; occupation: factory helper; entered dispensary, Jan. 9, 1917.

Diagnosis.—Chorea. Exostosis.

Complaint.—Mother states that patient has dropped dishes and knife and fork when eating. Facial distortion and funny motions with arms and legs since four weeks ago. At present patient is hardly able to walk. Patient has to be dressed, in fact put to bed and fed by her family.

Fig. 8.—Case 1, R. B. Tibial exostosis with compression of fibula.

History.—Patient and family have noticed during last few years lumps on different parts of body, especially left arm just below shoulder. These have caused no alarm and little attention. Patient has been unable to raise the left arm to comb her hair.

Past History.—Never has been ill.

Family History.—Parents alive and well. Negative.

Physical Examination.—Patient is noticeably short of stature, walks with a curious short step, automaton-like. Motion of arms and legs is decidedly limited. Skin is dark but clear. Lungs and heart are negative. The skeletal examination shows marked changes. Both large and small, more or less hard, irregular masses are felt on different parts of body, mainly near head of humerus, wrists, knees and ankles. Hands and feet are small and show difference in length of toes and fingers. More detailed information could not be obtained. Weight, approximately 100 pounds. Height, approximately 5 feet.

Roentgenographic Examination.—Skull: Diameters apparently within normal limits. There is no disproportion between the skull and face. Teeth show normal dentition. Sinuses are small. Bones in general of normal density. Tables of skull of normal width. Sutures, circulatory depressions and intercranial density within normal limits. Sella turcica is small. The clinoid processes closely approximate each other.

Vertebral Column: Cervical vertebrae within normal limits. Dorsal and lumbar vertebrae, although small, are well shaped, within normal limits. There is a slight lateral curvature lower dorsal region. The sacrum is small, vertebral diameter much increased. Density and outline irregular, but no definite exostoses seen.

Ribs: Show some bowing and increased downward angle from the vertebral articulation. The anterior ends of the bone are slightly irregular, somewhat enlarged and widened and there are definite exostoses on the first, second and third ribs, left. Thorax slightly cone-shaped, narrow. Vertebral diameter increased.

Clavicles: In general length and shape, clavicles appear to be normal. Ends, however, are considerably increased in width and are porous and irregular in outline. At least 4 cm. of the distal end of the right and 3 cm. from the end of the left are distinctly thinned. There is an exostosis, lower surface 3 cm. from the distal end on the right.

Scapulae: As far as can be determined show very few changes, except in the glenoid and axillary borders of both scapulae. These are irregular and there are definite periosteal elevations and exostoses on the right. On the vertebral borders of the left, at the lower end, there are exostoses also. Acromion ends are somewhat porous; on the left they are slightly enlarged.

Pelvis: Bones of the pelvis are small, flattened, somewhat distorted. Iliac crest shows some irregularity. The epiphysis is still ununited. The epiphyseal line is slightly irregular. Exostoses occur on both sides, middle upper. A small exostosis occurs on the left outer border just above acetabulum. Another small exostosis occurs on the right at the lower sacro-iliac synchondrosis inferior surface. The os pubis is very large; increased in width; irregular surface and in marked contrast to the os ischii. Small areas of periosteal elevation closely resembling exostosis are seen. At os ischii on the right, below the acetabulum anterior surface, is a small exostosis.

Humeri: Right humerus is 23.5 cm. in length; width of head through epiphyseal line 4 cm. Width of condyles 5 cm. Middle of shaft 2.5 cm. Left epiphysis 4.2 cm. Width of condyles 5 cm. Middle of shaft 1.8 cm. In the upper half of both bones the changes are marked. Bone is increased in width below the epiphyseal line. The outer border on the right is irregular and the cortex is not visible. The inner upper left border is also irregular. Definite exostoses occur on both the inner and outer surfaces; definitely on the shaft—on the right, 5 cm. and 8 cm. below the epiphysis and on the left, 3.5 and 7.5 cm. below the epiphysis. The upper half of both bones are but slightly porous and the processes distincty merged with the bone proper. The lower half of both bones appears to be normal.

Radii and Ulnae: Right, 17 cm. in length. Left, 14.3 cm. in length. Right ulna 20 cm. in length; left ulna 17.4 cm. in length. From these measurements it is evident that there is a great disproportion in length between the two arms (Fig. 9). Ends are enlarged but not to such a marked extent as in the tibiae and fibulae. Ulna is not as much affected as the radius. The shafts show some periosteal thickening and the ends are affected for a distance of (right upper) 3 cm., (right lower) 5 cm., (left upper) 3 cm., (left lower) 4.5 cm. Longitudinal penciling is beautifully demonstrated. The epiphyseal lines are very definite; the ends are not united except for the left lower radius where union has taken place and the epiphysis is just as much affected as the lower diaphysis. Small exostoses are seen on ends of all these bones. Joint spaces are clear. There is no bowing of the bones. The styloid processes are noticeably stunted and rounded.

Femora: Right: Total length of the bone from the head to the lower articular surface is 37.5 cm. Left is more difficult to determine but is approximately 38 cm. in length. The ends of the bone are affected for approximately 10 cm. above and below (on the right). On the left, the bone is affected for approximately the same distance. This leaves only about 15.6 cm. of the shaft unaffected. The greatest changes are seen in the neck which is tremendously increased in width (Fig. 10). The angle is diminished and the ends appear deformed. Numerous lines are visible indicating exostoses, some of which are considerably denser than the bone and others are transparent.

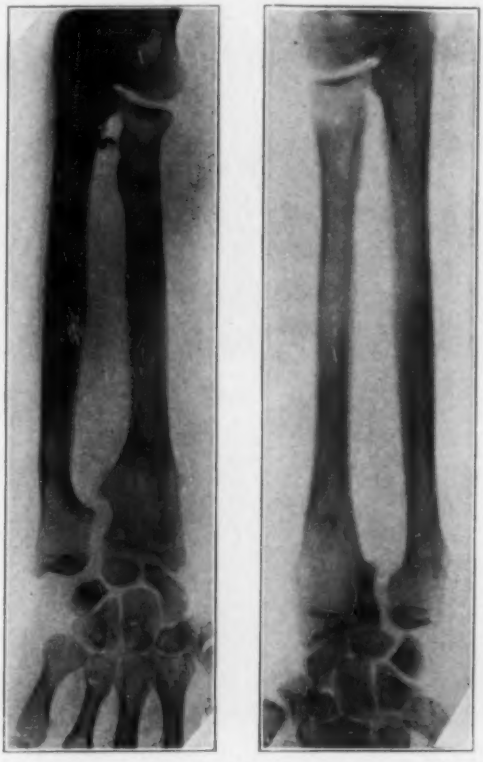


Fig. 9.—Case 2, E. D. Radius and ulna; no bowing. Marked disproportion of carpal bones.

Growths at the lower ends of the bone are mostly transparent. These growths are also somewhat different from the ones previously described as there seems to be a base line as heavy as the cortex in some instances, in which the growths distinctly arise. The middle of the right femur is 1.8 cm., the upper end is 6.3 cm. and the lower end 6.5 cm. wide. Left upper is approximately 8 cm. wide, lower 7.5 cm. Joint spaces and articular outlines are clear. Very few changes are seen in the lower epiphyses of the femora. The epiphyseal lines are discernible but not at the head of the femur. Some of the growths are apparently crowned entirely by cartilage as they gradually fade away on the roentgenograms. Lower end lateral view of femora shows some of these

exostoses to be enormous, with definite stalactite processes. Some of these growths are 3.5 by 5 cm. and the stalactite processes 5 cm. and more in length.

Tibiae and Fibulae: Right tibia: 29 cm. in length. Fibula 25 cm. in length. Left tibia 28.7 cm., fibula 25 cm. There is marked contrast between the ends of the bones and the shaft. For a distance of 10 cm. right upper, the tibia is much increased in width and on the left for a distance of 6 cm. Lower ends, approximatey 5 cm. of bone show the same changes (Fig. 11). The epiphyseal line is discernible but shows an increased deposit. In the areas affected the cortex is not discernible. The bones show beautiful penciling, longitudinal striations and the lateral surfaces show definite exostoses.

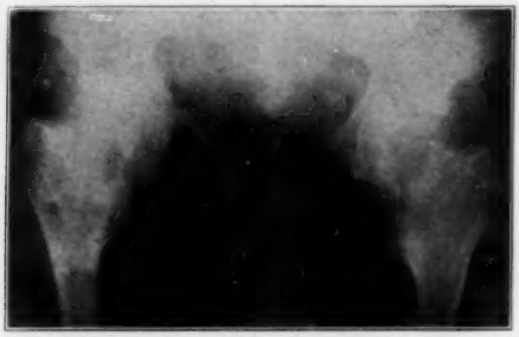


Fig. 10.—Case 2, E. D. Asymmetry of pelvis with enormous enlargement of upper end of femur.

Fig. 11.—Case 2, E. D. Lateral and anteroposterior views of lower end of tibia and fibula and tarsus. Exostoses on tibia and fibula. Disproportion of tarsal bones.

These are somewhat more transparent than the bone itself. These growths are not imposed on the cortex but appear to be part of the general growth of the ends. The fibulae show greater changes than the tibiae. The right fibula, middle of shaft, measures 1.2 cm. and the upper head 3.5 cm. The lower measures 3 cm. This increased width extends for 5 cm. above and 7 cm. below. The shaft is somewhat increased in width and there is some periosteal change at the ends of the bone. They show a greater increase in transparency and the lines run in all directions with superimposed lines from the growths. There is a definite irregular outline to the bone with definite exostoses. Left

fibula: The ends show greatest changes. The shaft is not as much affected. The width of the middle is 9-10 cm. The ends measure 4 cm. above and 2 cm. below. The upper end is affected for a distance of 5 cm. and is similar in appearance to the right. The lower end is less affected. The bones are not bowed. The epiphyses of the fibula do not show marked flattening or scarring. The lateral views simply exaggerate some of the points brought out in the antero-posterior description. Exostoses are somewhat more prominent.

Feet: Right: Changes are very slight in the bones of the feet. Some enlargement of the ends. The ends show slight periosteal swellings. Some disproportion in length of the metatarsal bones. Os calcis also shows slight periosteal and osteal changes. The left foot is more affected than the right. The greatest changes are seen in the os calcis, and in the third metatarsal. The os calcis shows rather prominent exostoses, some transparency of the bone and definite penciling, also lack of development in the bones as a whole. The third metatarsal is much shorter than the others. The shortening is approximately 1.5 cm. greater than in the other metatarsal bones. Large exostoses are seen at the distal end.

Fig. 12.—Case 2, E. D. Disproportion in length of metacarpals.

Carpals: Small, within normal limits.

Metacarpals: Right hand: Very short, rather broad, especially proximal fourth and distal third. The usual differences in length between the second, third, fourth and fifth metacarpals are lacking. The longest metacarpal is 4.8 cm. and the shortest is 4.3 cm. The first metacarpal, however, is 3.2 cm.

Left Hand: Here the differences in length are well marked. The bones are longer, contrast greater and the width not as marked as in the right hand. The second metacarpal is 5.8 cm. The fifth metacarpal is 3.5 cm. Some exostoses are evident on the second, fourth and fifth on the right, and on the third, fourth and fifth on the left. These growths are all at the distal end approximately 1.5 cm. to 1 cm. from the end. The ends of the bone both proximal and distal are quite porous. The cortex is solid, well formed (Fig. 12).

Phalanges: Show nothing unusual except for some increase in width of the proximal head and an exostosis on the fourth finger proximal phalanx 5 cm. from proximal end. Joint spaces are clear.

Case 3.—C. G., male, American, born in Connecticut, aged 16, single, occupation: tool maker, entered hospital June 24, 1917.

Diagnosis.—Genu valgum. Osteochondromata.

History.—All of his life patient has noticed lumps on various bones of body which have grown in the last six years. During the past few years patient has noticed that the right knee was becoming badly "knocked." Lumps are not painful.

Past History.—Scarlet fever at 4; no other sickness.

Family History.—Father and mother living and well; sister 3, living and well. No other members of family have any of these lumps.

Physical Examination.—Patient is a well developed and nourished boy. Skin: good color. Head: no masses or tender points on scalp. Ears: negative. Nose: negative. Eyes: pupils round, equal. React to light. Conjunctivae good color. Sclerae clear. Mouth: teeth in good condition. Tongue clear.

Fig. 13.—Case 3, C. G. Disproportion in length of thorax to lower extremities and marked curvature of right leg.

Pharynx: tonsils buried. Small white patch on right tonsil. No tumors about facial bones. Neck: negative. Thorax: no tumors of ribs. Abdomen: normal; no masses or tender points. Liver and spleen not enlarged. Genitalia: negative. Spine and pelvis: free from tumors.

Extremities: Scapulae and humeri free from nodules. Right forearm: the ulna is bowed backward, especially near its upper end (Fig. 13). There is a small cone shaped nodule near styloid process about 3 cm. in diameter. Near distal end, anterior surface of radius, is a nodule about 5 mm. in diameter. On dorsal surface of second, and third metacarpal bones, close to phalangeal joints, is a small nodule only about 3 mm. in diameter. None on fingers except nodule second phalanx, fourth finger, close to first phalangeal

joint. Small nodule dorsal surface inner border first phalanx little finger near proximal end. Nodule first phalanx, fourth finger near proximal end. Nodule on outer surface of thumb about half way between joints. The nodules on fingers are only a few millimeters in diameter.

Left Forearm and Hand: Similar bowing of left ulna though not so marked. Nodule on posterior surface of ulna 2 mm. in diameter and 3 cm. from tip of styloid process. On posterior surface of radius, close to inner border and 2 cm. from articular surface, is a very small nodule. On anterior surface of radius 2.5 cm. from lower end is a nodule 1 cm. in diameter. There is a small nodule on dorsal surface of second phalanx of middle finger close to first phalangeal joint. Small nodule on dorsal surface of first phalanx of index finger, about half way between joints. Small nodule on fourth finger, dorsal surface, close to metacarpal phalangeal joint. Small nodule on inner side dorsal surface of first phalanx little finger close to metacarpal phalangeal joint.

Right Thigh: In lower third outer surface of left femur is an irregular nodule (Fig. 14), 7 by 5 cm. On inner surface of femur just above condyle is a tumor 5 by 2 cm. These tumors are all firmly attached to bone; are very hard, not tender.

Right Leg: On inner side of tibia is an irregular mass 8 by 4 cm., reaching to within 3 cm. of upper end (Fig. 14). Small nodule on outer surface of fibula 5 cm. from upper end. There is a group of nodules of varying size, from 2 mm. to 1 cm. in diameter, just above malleolus. Similar group just above external malleolus.

Right Foot: No nodules. The third toe is much smaller than normal (Fig. 14).

Left Thigh: There is a nodule on anterior surface of thigh 1.5 cm. in diameter just above upper end of patella. On outer surface is an irregular mass 5 by 3.5 cm. beginning 5 cm. from lower end of femur (Fig. 14).

Left Leg: Small nodule on outer surface of fibula 5 cm. from upper end. Two nodules just above external malleolus. On inner surface of tibia close to upper end is an irregular group of nodules 9 by 5 cm. Group of nodules just above internal malleolus (Fig. 14). None on bones of feet.

There is marked genu valgum of right knee (Fig. 14).

Blood Examination.—Leishman's Stain. Ward IE, 7/30/17. Hemoglobin, 83 per cent; leukocytes, 5,760; polymorphonuclears, 180, 60 per cent.; lymphocytes, 88, 29 per cent.; transitionals, 22, 7.3 per cent.; eosinophils, 2, 0.7 per cent.; basophils, 1, 0.3 per cent.; myelocytes, 2, 0.7 per cent.; neutrophils, 2, 0.7 per cent.; pathologic lymphocytes, 3, 1 per cent.; total, 300; 99.7 per cent. Red blood cells: (1) some slight anisocytosis; (2) no poikilocytosis; (3) no nucleated red or basophilic cells; (4) platelets apparently normal in number.

Urine Examination.—June 25, 1917: specific gravity, 1.027. Otherwise negative.

Roentgenographic Examination.—Skull: Diameters appear to be within normal limits. Shape and general proportions of the skull as compared with the face and jaw bones within normal limits. Tables are thin. The sutures are not evident. There is no evidence of fontanels and the circulatory depressions are fairly discernible. Sinuses are very large and transparent. The sella turcica is within normal limits. The maxillary sinus is very large and irregular in outline. There is a small exostosis at the anterior nasal spine of the superior maxilla bone. The mandible is well formed. Shows an unerupted impacted molar. The bones forming the orbit are very irregular in outline.

Vertebral Column: Cervical region: vertebrae are small, delicately formed but within normal limits. The dorsal vertebrae are also within normal limits. There is a definite exostosis of the sacral region posterior and left lateral portions.

Ribs: Thorax is very narrow and long. The ribs are very thin, poorly developed, narrow in width and show considerable bowing. Downward angles

are increased and there is great disproportion in the width of the anterior rib spaces posteriorly and anteriorly. There is much increase in width of the anterior ends and definite exostosis occurs on the right fourth rib and on the left second rib front.

Clavicles: Right shows slight bowing. The left is straight. Length of left clavicle is approximately 30.5 cm.; right 14 cm. Right shows the greatest changes, ends are much increased in width and the distal end shows a definite exostosis with considerable transparency and penciling of the bone. There is periosteal thickening of both bones.

Fig. 14.—Case 3, C. G. On outer side of both femurs and inner side of both tibiae above and below are small nodules. The middle toe on the right foot is much smaller in proportion than the other toes.

Scapulae: Are small, but the acromion processes are very large. They are increased in width, transparent and show penciling. The ends are irregular. Scapulae outline is slightly irregular and there are definite exostoses occurring on the vertebral margin and just below the glenoid fossae on the left.

Pelvis: For the length of the femur, the pelvis is small, irregular in shape and with irregular surface outline. There are numerous exostoses and growths on the iliae, also on the os pubis. Os pubis is considerably deformed, increased in width and the symphysis pubis is increased in width also. Pelvic cavity is decreased in size, although fairly symmetrical. It is very difficult to determine the sacro-iliac synchondrosis on account of its extreme irregularity. The os ischii are also bowed and deformed.

Radii and Ulnae: Only the lower third of these bones was obtained. There is evident bowing and the ulna is shorter than the radius. The lower end of the ulna does not approximate the carpal bones within 1 cm. Ends of both bones are increased in width and there are definite exostoses just proximal to the epiphyseal line, and also a very large exostosis on the right radius 5 cm. above the lower end. Most of these exostoses appear to be a definite part of the bones themselves. A good deal of penciling and transparency may be seen at the lower ends of the radius and ulna, and part of the epiphyseal line is evident. The styloid processes are rounded and shortened. Joint space is clear.

Humerus: Only a small portion of the humerus shows. Approximate length of the left is 30 cm.; right not obtained. Width of the upper half apparently increased and there are definite exostoses visible at the inner border on the right 6 cm. from the epiphyseal line, and on the left 12 cm. from the upper epiphyseal line. The epiphyseal line is evident and the epiphysis somewhat flattened, enlarged, transparent and with typical penciling.

Fig. 15.—Case 3, C. G. Enormous bony growths on lower ends of the femurs.

Femora: Approximate length of the right and left femur is 50 cm. Bones are affected from the head for a distance of approximately 13 cm. and the ends for approximately 15 cm. The bones are equally affected. There is marked disproportion between head, neck and shaft. Neck is enormously widened but the whole upper end as well as the lower is extremely massive and club-like. The greatest width of the right is 8 cm. above and 9 cm. below. The left is 8.5 cm. above and 10 cm. below. The shaft (right) is 2.5 cm. and the left is 3.3 cm. No definite exostoses, although the increased growth gives an irregular outline to the whole bone. The lower ends, however, show enormous stalactite growths one of which shows a beautiful cauliflower process at its terminal end (Fig. 15). This particular growth is some 9 cm. long and its greatest width is 25 cm. The bone is not particularly transparent. Longitudinal lines, however, are evident, although somewhat dense. The epiphyseal lines are also evident but are irregular, not sharply outlined in form, shape or outline. There are no growths, masses or bone changes. The joint spaces are clear (Fig. 16).

Tibiae and Fibulae: The changes here are remarkable. The ends of the bones are immense, with very irregularly formed exostoses, stalactite processes presenting a striking appearance (Fig. 16). The length of the right tibia is approximately 39.5 cm., of the left 39 cm. Right fibula somewhat difficult

to determine on account of the growths; the right is approximately 36 cm. in length and the left 36.5 cm. The width of the bones is impossible to determine on account of the fusing of the fibula with the tibia (Fig. 17). The total width of the two bones upper end, right, is approximately 10 cm., lower end 10 cm.; left approximately 11 and 6.5 cm. Right middle shaft of tibia 2.5 cm., left 3 cm. Right fibula 1.3 cm., left 1.3 cm. Except for 19 cm. of negative bone in the shafts of both tibiae and fibulae, the rest is definitely affected. The shafts, however, show periosteal thickening. There are enormous coarsely formed exostotic growths. The bone itself (ends) shows heavy longitudinal lines, not very transparent. Epiphyseal lines are irregular and barely discernible. The heads of the tibiae show squaring, flattening and some widening (Fig. 16). Joint spaces are apparently clear. The lateral views add nothing to the picture except the transparency is somewhat more apparent and in irregular and more or less circumscribed area. Some of the growths are continuous with the bone proper and others apparently have arisen from the cortex (Fig. 18).

Fig. 16.—Case 3, C. G. Femurs, tibiae and fibulae showing growths on diaphysis and epiphysis.

Carpals: RIGHT: except for some transparency and penciling of the bones and slightly irregular form, the bones are negative.

Metacarpals: They differ in length and are disproportionate. The longest bone on the right is the third metacarpal which is 6 cm. and the shortest is the first metacarpal which is 4.3 cm. The second measures 5.7 cm., fourth 5.6 cm. and the fifth 5 cm. The proximal head shows the greatest widening, while both ends show transparency and irregular form with slight exostoses on the second and fifth bones. The distal epiphyseal lines are very evident as also the proximal epiphyseal line of the first metacarpal. There are also periosteal changes in shafts of the second and fifth metacarpals.

In the left hand the longest bone is the second metacarpal which measures 6.5 cm., while the first and fifth are equal in length, being 5.4 cm. The third is 6 cm. and the fourth is 5.5 cm. The changes are similar to those in the other hand, the only exception being the third matacarpal which is most affected. The interesting point in the matacarpals of both hands is that the distal epiphyses show these changes. The greatest changes are seen on the ends of the bone 1 cm. and less from the epiphyseal line.

Fig. 17.—Case 3, C. G. Disproportion in development of both tibiae and considerable bowing of the right tibia.

Fig. 18.—Case 3, C. G. Lateral view of lower end of tibia showing outline of growth continuous with bone growth.

Phalanges: Also show disproportion in length. The right hand shows the proximal phalanx of the second, third and fourth digits to be of the same length while the left shows the second to be shorter than the third and fourth. The flaring of the shafts and periosteal changes and the increase in width with slight exostoses is the same as described in the other cases. The epiphyseal lines are sharply demarcated and well discernible. There are definite exostoses on several of the phalangeal bones. The joint spaces are clear. There are no marked deformities.

Feet: Lateral views only. These show the greatest changes in the metatarsals which are bowed, irregular in outline, enormously increased in width at the proximal and distal ends with definite exostoses on several of the bones. There is also some transparency and pencilling, mostly of the proximal portions. The tarsal bones show beautiful penciling and an increased transparency. The os calcis is large and well developed, whereas the astragalus is well developed, small. The growths are exaggerated and the portions are disproportionate in size. There are also periosteal changes. No definite exostoses. The joint spaces are sharply outlined and perfectly clear.

Fig. 19.—Case 4, R. W. H. The disproportionate shortness of the lower legs is well shown.

Case 4.—R. W. H., born in South Carolina; age 31, male, single; occupation: till 19 on farm and then clerk and bookkeeper. Lived in South Carolina all his life. Average weight, about 114 pounds. Examined, June, 1918 (Fig. 19).

Family History.—Grandmother, father's side, died of old age, 69 years; grandmother, mother's side, died at 33, cause unknown; grandfather, father's side, killed in Civil War; grandfather, mother's side, died of old age, 79 years.

Mother died at 38 from pneumonia. Father living at 62 in good health. Tall. On mother's side all of good size. She, however, was quite short in comparison to others. Two uncles, both healthy, but younger of two is similar in stature to patient. Four aunts, nothing abnormal. One brother alive and well, 70½ inches in height. Three sisters alive and well. One sister died of tuberculosis at 18. Four half brothers born after second marriage of father; all alive and well with exception of one who is similar to patient in stature, but very strong. One half brother died probably of typhoid fever. Three half sisters all healthy. Seven nieces all alive and well; three nephews alive; two are well, one has peculiar throat trouble, otherwise well. One nephew died in childhood, cause unknown. All normal in size. Mother and father were third cousins. Second marriage no relationship at all. Family diseases—no cancer; no heart disease; no "rheumatism;" no pellagra; no hookworm. Tuberculosis in one sister, an aunt and three of her children.

Past History.—Breast-fed till 1½ years old, then usual table diet. (Breakfast: Meat, corn mush, butter and syrup, flourbread. Noon: Vegetables, milk, bread and butter, pie, corn bread. Supper: Rarely meat, milk, butter, corn bread and butter, fruits and milk. Corn bread was quite commonly used.) Diseases: Measles, whooping cough, mumps, malaria (?). Mildest kind of attacks. No "stomach trouble" in childhood. In 1912 a nervous breakdown with gastric disturbances. Pain in epigastrium after meals and between meals. Pain was general and not related to meals; occasionally when without meals. Never vomited. No bowel disturbances. Always able to work and gained in weight during his illness. Venereal History: Gonorrhea in 1916; duration one year; treated and cured. Syphilis denied. No history of secondaries.

Present History.—At 6 years father noticed enlargement on inside of right ankle. Was treated with iodin locally. No diagnosis made. Within two years the other ankle showed enlargement. There was no pain or difficulty in walking. From time to time, until 10 years of age these lumps were discovered all over the body, especially under left arm, in axilla, and on ribs. Since that time, between the ages of 10 and 15 they appeared on lower extremities and after an injury to left hip on that region. During this time fell on coccyx and a mass developed there; this, however, was somewhat softer than the others. Met with no other accidents; never had any fractures. Last one noticed was on the outer side of the right thigh, at age of 23, following a fall two years before, at which time he had distinct ecchymoses. Never penetrated skin. Has noticed certain ones disappear under arm, on left wrist and little one on thumb. One on wrist disappeared five years after first noticed, when he was 14 years old. Size was about that of a half-dollar and elevated skin about a quarter of an inch. Chief complaint: Limitation of motion, lower limbs only. Cannot bend and reach feet normally and is handicapped on hikes and in calesthenics. Otherwise no discomfort. Urine and blood examination of no interest.

Roentgenographic Examination.—Skull: Diameters within normal limits. The proportions of the face are comparable to those of the skull. Teeth show normal dentition. Sinuses within normal limits. The bones are of normal density except for the mala and zygoma which are larger and heavier, slightly more irregular than normal. Tables of the skull, posterior half show increased width, are denser and the internal and external surfaces show some irregularity. Sella turcica is fairly large, within normal limits. The sutures, circulatory depressions and intercranial density within normal limits.

Vertebral Column: Cervical vertebrae irregular in shape and form. Surface is also somewhat irregular. There are no definite exostoses. The dorsal portion shows a definite double lateral curvature. Vertebrae, are well formed.

Ribs: The ribs are considerably more bowed on the right than on the left. Downward angle of both sides increased. Rib spaces are very narrow. Thorax is definitely asymmetrical. Anterior ends are increased in width and are somewhat irregular.

Phalanges: Also show disproportion in length. The right hand shows the proximal phalanx of the second, third and fourth digits to be of the same length while the left shows the second to be shorter than the third and fourth. The flaring of the shafts and periosteal changes and the increase in width with slight exostoses is the same as described in the other cases. The epiphyseal lines are sharply demarcated and well discernible. There are definite exostoses on several of the phalangeal bones. The joint spaces are clear. There are no marked deformities.

Feet: Lateral views only. These show the greatest changes in the metatarsals which are bowed, irregular in outline, enormously increased in width at the proximal and distal ends with definite exostoses on several of the bones. There is also some transparency and pencilling, mostly of the proximal portions. The tarsal bones show beautiful penciling and an increased transparency. The os calcis is large and well developed, whereas the astragalus is well developed, small. The growths are exaggerated and the portions are disproportionate in size. There are also periosteal changes. No definite exostoses. The joint spaces are sharply outlined and perfectly clear.

Fig. 19.—Case 4, R. W. H. The disproportionate shortness of the lower legs is well shown.

Case 4.—R. W. H., born in South Carolina; age 31, male, single; occupation: till 19 on farm and then clerk and bookkeeper. Lived in South Carolina all his life. Average weight, about 114 pounds. Examined, June, 1918 (Fig. 19).

Family History.—Grandmother, father's side, died of old age, 69 years; grandmother, mother's side, died at 33, cause unknown; grandfather, father's side, killed in Civil War; grandfather, mother's side, died of old age, 79 years.

Mother died at 38 from pneumonia. Father living at 62 in good health. Tall. On mother's side all of good size. She, however, was quite short in comparison to others. Two uncles, both healthy, but younger of two is similar in stature to patient. Four aunts, nothing abnormal. One brother alive and well, 70½ inches in height. Three sisters alive and well. One sister died of tuberculosis at 18. Four half brothers born after second marriage of father; all alive and well with exception of one who is similar to patient in stature, but very strong. One half brother died probably of typhoid fever. Three half sisters all healthy. Seven nieces all alive and well; three nephews alive; two are well, one has peculiar throat trouble, otherwise well. One nephew died in childhood, cause unknown. All normal in size. Mother and father were third cousins. Second marriage no relationship at all. Family diseases—no cancer; no heart disease; no "rheumatism;" no pellagra; no hookworm. Tuberculosis in one sister, an aunt and three of her children.

Past History.—Breast-fed till 1½ years old, then usual table diet. (Breakfast: Meat, corn mush, butter and syrup, flourbread. Noon: Vegetables, milk, bread and butter, pie, corn bread. Supper: Rarely meat, milk, butter, corn bread and butter, fruits and milk. Corn bread was quite commonly used.) Diseases: Measles, whooping cough, mumps, malaria (?). Mildest kind of attacks. No "stomach trouble" in childhood. In 1912 a nervous breakdown with gastric disturbances. Pain in epigastrium after meals and between meals. Pain was general and not related to meals; occasionally when without meals. Never vomited. No bowel disturbances. Always able to work and gained in weight during his illness. Venereal History: Gonorrhea in 1916; duration one year; treated and cured. Syphilis denied. No history of secondaries.

Present History.—At 6 years father noticed enlargement on inside of right ankle. Was treated with iodin locally. No diagnosis made. Within two years the other ankle showed enlargement. There was no pain or difficulty in walking. From time to time, until 10 years of age these lumps were discovered all over the body, especially under left arm, in axilla, and on ribs. Since that time, between the ages of 10 and 15 they appeared on lower extremities and after an injury to left hip on that region. During this time fell on coccyx and a mass developed there; this, however, was somewhat softer than the others. Met with no other accidents; never had any fractures. Last one noticed was on the outer side of the right thigh, at age of 23, following a fall two years before, at which time he had distinct ecchymoses. Never penetrated skin. Has noticed certain ones disappear under arm, on left wrist and little one on thumb. One on wrist disappeared five years after first noticed, when he was 14 years old. Size was about that of a half-dollar and elevated skin about a quarter of an inch. Chief complaint: Limitation of motion, lower limbs only. Cannot bend and reach feet normally and is handicapped on hikes and in calesthenics. Otherwise no discomfort. Urine and blood examination of no interest.

Roentgenographic Examination.—Skull: Diameters within normal limits. The proportions of the face are comparable to those of the skull. Teeth show normal dentition. Sinuses within normal limits. The bones are of normal density except for the mala and zygoma which are larger and heavier, slightly more irregular than normal. Tables of the skull, posterior half show increased width, are denser and the internal and external surfaces show some irregularity. Sella turcica is fairly large, within normal limits. The sutures, circulatory depressions and intercranial density within normal limits.

Vertebral Column: Cervical vertebrae irregular in shape and form. Surface is also somewhat irregular. There are no definite exostoses. The dorsal portion shows a definite double lateral curvature. Vertebrae, are well formed.

Ribs: The ribs are considerably more bowed on the right than on the left. Downward angle of both sides increased. Rib spaces are very narrow. Thorax is definitely asymmetrical. Anterior ends are increased in width and are somewhat irregular.

Clavicles: Show considerable bowing and are enormously increased in width at the ends The right measures approximately 15 cm. in length. The proximal end is 3.5 cm. wide; distal end is 3 cm. wide. Middle of the shaft is only 1.5 cm. wide. The bones are affected for approximately 5 cm. from the ends leaving approximately 5 cm. unaffected. The left is also 1.5 cm. in length; 2.5 cm. wide proximal end, 1.8 cm. distal end; middle of shaft is 1.5 cm. Left consequently is not as much affected as the right. Definite exostoses and same changes described in the other bones are seen here.

Scapulae: Are decidedly small if compared with the acromion process and the humerus. Angles are increased; surfaces are irregular. Glenoid fossae are shallow and small. Acromion shows increased length and width—is also transparent, with considerable penciling. The distal surface is slightly irregular. The acromion clavicular junction is increased in width and the end of the clavicle does not fit as closely as in the normal. This is usually due to changes in the clavicle.

Fig. 20.—Case 4, R. W. H. Asymmetry of pelvis and large head, neck and trochanters of the femur.

Pelvis: Within normal limits as to general size, proportion and shape, except for changes in the os pubis, where the bones are somewhat irregular in outline and shape and show definite exostoses. They are increased in width and are well contrasted to the os ischii. Definite exostoses left ilium midportion, superior posterior surface. Outlines of the bones in general are irregular. Bones are not transparent. There is a slight asymmetry of the pelvis as a whole (Fig. 20).

Radii and Ulnae: Bones of both forearms are curved (Fig. 21). Surfaces are irregular. The ends of the bones are considerably more porous than usually. The cortex is not visible in several areas. The middle of the shafts shows the medullary canal to be considerably occluded. In the right the radius from the head to the tip of the styloid process is 23.4 cm. and on the left is 23.7 cm. Right ulna from the tip of the olecranon process to the tip of the styloid process is 23.9 cm. On the left, the ulna is 22.9 cm. The width of the shaft of the radius, right, is 1.6 cm. and left 1.7 cm. The width of the ulna, right, is 2 cm. and left 1.5 cm. Greatest changes are seen at the ends of the bones approximately 7 cm. from the lower end of the right radius and approximately 6.5 cm. from the lower end of the left. The proximal ends of

the ulna, however, show the greatest changes. The heads and the coronoid processes are increased in width, are very porous and irregular in outline. The epiphyseal lines are practically indiscernible. The epiphysis and diaphysis appear as one bone. There are definite exostoses, the largest being on the right 5 to 7.5 cm. from the lower end adjoining the ulna. The shape of the ends of the bone is considerably distorted, blunted and rounded. Joint spaces are clear.

Femora: Right: Length of the femur approximately 15 cm. Width, right upper, approximately 9.5 cm., lower 9 cm.—if including the exostoses 10.5 cm., middle of shaft 2.5 cm. Left: Length of left femur approximately 19 cm. Width, left upper 9.5 cm., left lower 9.5 cm., middle of shaft 2.5 cm.

The bones are affected for approximately all but 18 cm. of the shaft. Ends of the bones appear as massive clubs, irregular in form and outline, with definite large round and stalactitelike processes (Fig. 22). Some of these have

Fig. 21.—Case 4, R. W. H. Considerable bowing of the radius and ulna; disproportionate growth in length; rounded styloid and exostoses.

undergone complete ossification. There is great lack of proportion between the neck, head and shaft. The epiphyseal lines are not discernible. The lower ends show no cortex and the growths are apparently continuous with the growth of the bone and show distinct longitudinal penciling with transparency. The shape of the lower epiphysis is within normal limits and the joint space is clear.

Humeri: Right is approximately 35 cm. long, left is 33 cm. long. Right does not show as much change as the left. The head is 6 cm. in width as compared with 3 cm. for the middle of the shaft. This last measurement, however, is increased because of a definite round periosteal thickening. The cortex is visible throughout and only slight changes are seen in the middle

Clavicles: Show considerable bowing and are enormously increased in width at the ends The right measures approximately 15 cm. in length. The proximal end is 3.5 cm. wide; distal end is 3 cm. wide. Middle of the shaft is only 1.5 cm. wide. The bones are affected for approximately 5 cm. from the ends leaving approximately 5 cm. unaffected. The left is also 1.5 cm. in length; 2.5 cm. wide proximal end, 1.8 cm. distal end; middle of shaft is 1.5 cm. Left consequently is not as much affected as the right. Definite exostoses and same changes described in the other bones are seen here.

Scapulae: Are decidedly small if compared with the acromion process and the humerus. Angles are increased; surfaces are irregular. Glenoid fossae are shallow and small. Acromion shows increased length and width—is also transparent, with considerable penciling. The distal surface is slightly irregular. The acromion clavicular junction is increased in width and the end of the clavicle does not fit as closely as in the normal. This is usually due to changes in the clavicle.

Fig. 20.—Case 4, R. W. H. Asymmetry of pelvis and large head, neck and trochanters of the femur.

Pelvis: Within normal limits as to general size, proportion and shape, except for changes in the os pubis, where the bones are somewhat irregular in outline and shape and show definite exostoses. They are increased in width and are well contrasted to the os ischii. Definite exostoses left ilium midportion, superior posterior surface. Outlines of the bones in general are irregular. Bones are not transparent. There is a slight asymmetry of the pelvis as a whole (Fig. 20).

Radii and Ulnae: Bones of both forearms are curved (Fig. 21). Surfaces are irregular. The ends of the bones are considerably more porous than usually. The cortex is not visible in several areas. The middle of the shafts shows the medullary canal to be considerably occluded. In the right the radius from the head to the tip of the styloid process is 23.4 cm. and on the left is 23.7 cm. Right ulna from the tip of the olecranon process to the tip of the styloid process is 23.9 cm. On the left, the ulna is 22.9 cm. The width of the shaft of the radius, right, is 1.6 cm. and left 1.7 cm. The width of the ulna, right, is 2 cm. and left 1.5 cm. Greatest changes are seen at the ends of the bones approximately 7 cm. from the lower end of the right radius and approximately 6.5 cm. from the lower end of the left. The proximal ends of

the ulna, however, show the greatest changes. The heads and the coronoid processes are increased in width, are very porous and irregular in outline. The epiphyseal lines are practically indiscernible. The epiphysis and diaphysis appear as one bone. There are definite exostoses, the largest being on the right 5 to 7.5 cm. from the lower end adjoining the ulna. The shape of the ends of the bone is considerably distorted, blunted and rounded. Joint spaces are clear.

Femora: Right: Length of the femur approximately 15 cm. Width, right upper, approximately 9.5 cm., lower 9 cm.—if including the exostoses 10.5 cm., middle of shaft 2.5 cm. Left: Length of left femur approximately 19 cm. Width, left upper 9.5 cm., left lower 9.5 cm., middle of shaft 2.5 cm.

The bones are affected for approximately all but 18 cm. of the shaft. Ends of the bones appear as massive clubs, irregular in form and outline, with definite large round and stalactitelike processes (Fig. 22). Some of these have

Fig. 21.—Case 4, R. W. H. Considerable bowing of the radius and ulna; disproportionate growth in length; rounded styloid and exostoses.

undergone complete ossification. There is great lack of proportion between the neck, head and shaft. The epiphyseal lines are not discernible. The lower ends show no cortex and the growths are apparently continuous with the growth of the bone and show distinct longitudinal penciling with transparency. The shape of the lower epiphysis is within normal limits and the joint space is clear.

Humeri: Right is approximately 35 cm. long, left is 33 cm. long. Right does not show as much change as the left. The head is 6 cm. in width as compared with 3 cm. for the middle of the shaft. This last measurement, however, is increased because of a definite round periosteal thickening. The cortex is visible throughout and only slight changes are seen in the middle

and in the inner upper ends approximately 10 cm. from the head. Epiphyseal line is fairly well seen. The lower end of the bone shows very slight changes, some increase in width, some periosteal change and decided transparency. Right no greater, however, than the left. Left: Head is 5.7 cm. wide and 10 cm. below this it is 4.5 cm. wide. Bone is affected for a distance of 16 cm. Definite exostoses with marked cortex, medullary and periosteal changes are seen. The lower end is practically unaffected. Epiphyseal line not determined. In both cases there is lack of contrast between the surface, neck and the shaft. Joint spaces are clear.

Tibiae and Fibulae: The most striking changes are seen in the tibiae and fibulae. Ends are fused together. In the case of the left lower tibia and fibula which appear as one bone, middle of fibula is almost as wide as the tibia (Fig. 23), being 1.7 cm. as compared to 2.5 cm. on the right and the

Fig. 22.—Case 4, R. W. H. Enormous growths of different types on both the upper and lower extremities of the femur.

left 1.7 cm. as compared to 2.3 cm. There is no division line. Longitudinal lines are transparent and continuous throughout. Right tibia is 36 cm. in length; fibula is 33 cm. in length (Fig. 24). Left tibia 34 cm. in length and the fibula 31 cm. Greatest width of right tibia is approximately 8 cm. above and 5 cm. below and 2.5 cm. in middle of shaft. The fibula cannot be determined on account of its enormous growth. Left tibia is approximately 7 cm. wide above, but cannot be determined below. The total width of the tibia and fibula is 5.5 cm. Practically the entire diaphysis is affected except for an area not greater than 10 cm. on the right and 8.5 cm. on the left. Fibula appears affected throughout. There is marked transparency of the ends.

Throughout the whole bone beautiful longitudinal penciling is seen. The epiphyseal line is not discernible. The upper epiphyses of the tibia are flattened, square and somewhat irregular in shape.

Carpals: There is considerable disproportion between the various carpal bones of both hands. Capitate is very large and the lesser multangulum is very small. The greater multangulum appears to be fused with the lesser multangulum. This is also true of the capitate with the hamate bones. The trapeziform bone on the right shows a definite exostosis (Fig. 25).

Fig. 23.—Case 4, R. W. H. Lateral view of the tibiae and fibulae showing distribution and types of new growths.

Metacarpals.—Show a marked disproportion in size in both hands. The right longest bone is the third metacarpal which measures 6 cm. and the shortest is the fifth which measures 4.5 cm. The first and fourth measure 4.6 cm. On the left the longest bone is the second metacarpal which measures 6.7 cm. and the shortest is the first metacarpal which measures 4.2 cm. The fifth is 5 cm. long, the fourth, 5.5 cm. and the third, 6.3 cm. Heads of both proximal and distal are enlarged and show considerable porosity. There is, however, no deformity of the metacarpals on the left but on the right the second, fourth and fifth are deformed. Exostoses appear approximately 2 cm. from the distal end (Fig. 25).

Fig. 24.—Case 4, R. W. H. Anteroposterior view of tibiae and fibulae showing growths on both bones and disproportionate development.

Fig. 25.—Case 4, R. W. H. Variation in length and size of carpals and metacarpals; deformity of wrist.

Phalanges: There are considerable changes in the phalanges of both hands. For the most part, the bones are porous, the cortex well outlined, the bones increased in width and the surfaces considerably irregular. There are also definite small exostoses seen on eight of the bones in the different fingers (Fig. 25). Wherever there is an exostosis the porosity of the heads apparently continues with the exostosis.

Feet. Right: Changes in the metatarsals are as marked as those seen in the metacarpals. The second metatarsal is only 5 cm. in length, the first being 6.3 cm., the third, 7 cm., the fourth, 6.5 cm., and the fifth, 6 cm. The left metatarsals do not show the same changes. The ends of the bones are increased in width and the epiphyseal lines are not evident. Marked transparency and beautifully pencilled longitudinal lines are seen and definite small exostoses occur. The same changes are noticeable in all of the phalanges.

The tarsal bones, except for their greater transparency and penciling, show very slight changes. Joint spaces are clear.

DISCUSSION

From a study of these four cases it is evident that the flat bones, that is, the scapulae, iliae, ribs and even the skull bones, are frequently affected and to quite an extent. The long bones, although markedly affected in most cases, may, in some cases, present very little change. This is quite noticable in the humerus. In general, the femur, tibia and ulna bones show the greatest growth changes, and, on the other hand, the vertebrae and facial bones show the least, often no changes at all.

TABLE 1.—The Length of Metacarpal Bones. The Measurements in Four Cases of Exostosis are Compared with the Average in Twenty Adult Cases

	Right Hand					Left Hand				
	1	2	3	4	5	1	2	3	4	5
Normal	4.5	6.7	6.7	5.4	5.5	4.9	6.5	6.7	6.0	5.5
Case R. B.	4.0	6.2	5.7	5.8	5.0	4.2	6.5	6.3	5.5	5.4
Case E. D.	3.2	4.7	4.9	4.5	4.4	3.6	5.8	5.3	3.9	3.5
Case C. G.	4.3	5.7	6.0	5.6	5.0	5.4	6.5	6.0	5.5	5.4
Case R. W. H.	4.6	5.5	6.0	4.6	4.5	4.2	6.7	6.3	5.5	5.0

The changes in the bones can best be studied under two heads. Those affecting growth, that is, form, length and size, with relative changes in periosteum, osteum and medullary canal, and those showing proliferative and inflammatory-like changes.

Growth retardation can best be seen in the metacarpal bones. We have in the normal fairly definite lengths and comparative sizes for the different metacarpal bones and these run fairly true (Table 1). In our cases there is marked variance in the length, form and size of the different metacarpals in the single hand and most strikingly so when the two hands are compared. These changes must necessarily have begun very early in life to be of so pronounced a type at present. They are not retrogressive processes on the part of some bones and

progressive processes on the part of other bones. The carpal bones show fairly marked changes but mostly in size and form. It is difficult to judge whether such changes may not be due partly to pressure between the long bones of the forearm and fingers, resulting on the one hand in definite excessive growth and on the other in retardation of growth.

Similar changes are seen in the scapulae, the pelvic bones, the metatarsals and to some extent in the tarsal bones. In the scapulae the disproportion between the body of the bone and the acromion process is very noticeable; the acromion process is exceedingly large, the body and the glenoid process small. When the head of the humerus is enlarged, as it invariably is, the smallness of the glenoid cup is striking. Changes in the growth of the bones are also seen in the ulna, radius and fibula. These changes are of a different type, however, and are not so consistently present. In the case of the radius and ulna one of the most interesting points is the absence very often of the styloid process. This gives evidence, therefore, of the very early changes that occur in this disease.

Changes in growth may frequently involve only part of a bone or one bone in a group, such as is seen in the femur where the head, neck and trochanters are affected and the shaft and condyles are apparently unaffected or in the case of the wrist bones where the os magnum may be markedly large in comparison with the other carpal bones, or, again, in the case of the phalanges where the proximal or middle phalanx may be unusually short as compared with the apparently normal length of the other two phalangeal bones.

In the majority of bones the normal length has been reached, and growth has been retarded only in respect to their size. The ribs, for instance, are abnormally delicate and symmetrical, but their length compares favorably with the normal. The radii in some portions may show a very small diameter as compared with the other bones of the skeleton or with the normal, but this is quite a different process. In the case of the ribs there are no marked growths, no enlargements or compensation in growth in one part as compared with another, but, in the case of the radii it is conceivable that the lack of growth in one part may be due to the excessive growth in another. It is suggested, therefore, that when the length of the bones is not interfered with, there may be one of two causes, either the epiphyses are unaffected in early life or the growth, such as is seen in the heads and neck of the femur, occurs later in life when the growth in length of bone has been reached. If this is conceded, then there are dissimilar processes going on in different bones either at the same time or at different periods of growth.

A study of the location or site of the growths or processes demonstrates two main facts, that they occur both distal and proximal to the epiphyseal line and that the two processes may be entirely dissimilar. The growths or enlargements at the epiphyses may be extended downward so as to be continuous with the process on the diaphysis or they may be separated. It is frequently difficult to determine to just what point the process extends as the changes from the gross to the minor are so gradual and often very variable. For instance, the growth at the epiphyses may be of a large, diffuse proliferative type affecting all portions of the bone and just below this may occur changes in cortex and periosteum within regular bounds and finally lower down there may be a purely periosteal reaction, similar to any inflammatory periosteal reaction. Frequently, the epiphysis is affected, showing a fairly intact epiphyseal line with no change in the ends of the diaphysis, but a definite, more or less localized periosteal and slight osteal growth is seen on the diaphysis proper, probably at its middle. This last point suggests another process, perhaps not directly and primarily related to the epiphyseal processes.

A study of the growths demonstrates, further, the differences alluded to above. For the sake of a clearer understanding of the matter, these are divided into three groups:

a. *The Epiphyseal Changes.*—The epiphyseal changes are mainly enlargements and distortions of form and vary considerably in the different bones. In the femur I have seen no growths on the head, but the great trochanters show frequent large irregularities. The femur shaft from just below the trochanters to the articular surface is so large and irregular in form as to bear little or no resemblance to the normal femur. The neck is double the diameter of the head, instead of presenting the usual constriction between head and trochanter. The cancellous lamellae do not run in well formed continuous lines, but in criss-cross directions, and in interrupted lines. These lines may be heavier and denser than the normal or, if much absorption has taken place, then in delicate pencilled lines. The condyles of the femur are enlarged, rather hypertrophied; the form becomes more or less square, the surfaces flattened. The longitudinal diameter is increased to twice the normal and the interlamellae spaces are much increased in size, consequently the bone is more transparent than the normal. I have seen no growths on the condyles, although growths occur just at the epiphyseal line. The head of the tibia shows the same changes as the condylar end of the femur. The fibula head and the acromial process of the scapula are distinct exceptions. Here definite growths occur, and these are epiphyseal in origin. The vertebral border of the scapula also shows growth. The metacarpals, meta-

tarsals and the phalanges are also exceptions. The epiphyseal ends here are early affected, changes in form and outline with distinct growths developing before puberty.

Table 2 gives the dates at which ossification of the epiphyses and their union to the shafts of the bones become recognizable by means of roentgenography. It is for use in comparison with four cases of multiple cartilaginous exostosis.

TABLE 2.—Time of Recognition of Ossification of Epiphyses and Their Union with Shaft by Means of Roentgenography

	Normal		Cases			
	Time of Appearance of Epiphysis	Time of Union with Shaft	B, 22 Yrs.	D, 16 Yrs.	G, 16 Yrs.	H, 31 Yrs.
Clavicle	18th to 20th year	22d to 25th year	e	e	e	e
Humerus:						
Head	3d to 4th month	20th to 25th year	e	dl	—	e
Great tuberosity	2d year		e	dl	—	e
Lesser tuberosity	3d year					
Lower epiphysis			e	?	—	e
Capitellum	End of 2d year	18th year	e	e	e	e
Trochlea	10th to 13th year		e	e	e	e
External epicondyle	12th year		e	?	e	e
Internal epicondyle	5th year		e	?	dl	e
Radius:						
Head	5th to 6th year	16th to 19th year	e	e	dl	e
Lower epiphysis	2d to 3d year	17th year	e	dl	dl	le
Ulna:						
Olecranon	10th to 13th year	20th to 21st year	e	e	e	e
Lower epiphysis	5th to 7th year	20th to 24th year	e	dl	dl	e
Styloid process	4th year	20th to 24th year	e	e	e	e
Metacarpals:						
Thumb (base)	7th to 8th year	16th to 20th year	e	e	dl	e
Other digits (heads)	4th to 6th year	16th to 20th year	e	e	dl	e
Phalanges	4th year	18th to 20th year	e	e	dl	e
Femur:						
Upper epiphysis	Shortly after birth	18th to 22d year	e	e	dl	e
Great trochanter	4th to 5th year	18th to 22d year	e	e	dl	e
Lesser trochanter	13th to 14th year	17th to 22d year	e	e	e	e
Lower epiphysis	9th fetal month	22d to 24th year	e	e	dl	e
Patella	3d year		e	e	e	e
Tibia:						
Upper epiphysis	9th fetal month	18th to 24th year	e	le	dl	le
Lower epiphysis	1st to 2d year	16th to 18th year	e	le	dl	e
Tubercle (if separate)	12th to 13th year	18th to 24th year	...	...	...	e
Fibula:						
Upper epiphysis	4th to 5th year	20th to 22d year	e	...	dl	e
Lower epiphysis	2d to 3d year	21st to 23d year	e	le	dl	e
Metatarsals	3d to 8th year	16th to 19th year	e	e	dl	e
Phalanges	5th to 8th year	18th to 20th year	e	e	few	e
Epiphysis of os calcis	7th to 10th year	16th to 18th year	e	e	e	e

Explanation: e, complete, no evidence of epiphyseal line; le, incomplete, line still evident; dl, definite epiphyseal space vacant.

The most striking epiphyseal changes, perhaps, are those of the fibula and acromion. In both these bones it is of importance to note that the bodies themselves suffer in length and size just as occurs in the metacarpal bones. In the case of the fibula early fusion with the tibia may play a part in retarding growth of the bone.

Changes, therefore, occurring in the epiphysis of the bones may be metaplastic but under control, metabolic or may appear as unrestricted growths.

In studying epiphyseal changes, one of the most striking features is the early disappearance of the epiphyseal lines or space, but this is by no means constant, even in the bones of a single case (Table 2). Two of the patients were only 16 years of age, so it is presumed that ossification and union took place a year or more previously, judging from the density of the bones and the total absence of an epiphyseal line. This may be due to the growths either directly or indirectly by pressure, or it is even possible that if a longitudinal section were made through the epiphysis, traces of an epiphyseal line would still be seen. This fact, therefore, has an important bearing on the growth of the bone and would apply to the marked changes seen in the fibula and also the bones of the forearm. In the case of the tarsals, metacarpals and phalanges it can have little bearing, as retarding influences must have been present long before epiphyseal factors played a part.

b. *Changes at the Diaphyseal Ends.*—The greatest and most common changes occur at the ends of the shaft adjacent to the epiphysis. In the lower ends of the femurs and in both ends of the tibia the changes are most striking. They may encroach on the epiphysis (Fig. 26), but they originate on the diaphysis. These growths affect the bone itself. The ends are enormously enlarged, irregular in shape and outline, giving rise to curiously shaped outgrowths, some stalactite in type, five and more centimeters in length and two and more in diameter. The terminal portions are often cauliflowerlike, with areas of irregular transparency, indicating incomplete cartilaginous ossification and other areas denser than the normal bone. They grow in all directions, mainly, however, longitudinal and parallel to the bone, suggesting progress in the direction of least resistance. It is also possible that muscular movement, since small areas of muscle attachment appear on the growth, may sufficiently irritate to excite further growth of these projections. They also apparently have a great tendency to deposit calcium. There is no base to these growths. The cancellous lamellae of the bone are often continuous with the growth. They apparently represent changes originally of the bone itself. Frequently, cortex and an inner canal of a different bone structure can be seen in the growth. The part of the diaphysis affected often shows no cortex, no medullary narrow canal and the bone structure apparently is much disorganized. These growths may interfere with joint movement, such as a growth on the tibia exerting such pressure on the fibula as to interfere with its development (Fig. 26). The excessive bone growth of the diaphysis in one part may affect the growth of the bone in another part. Bowing of the shaft frequently seen, suggests unequal growth, as in the case of forearms or lower legs. These points suggest the very early changes that occur in the bones themselves.

c. *Exostosis and Periosteal Growths.*—In quite a number of bones two types of changes appear apart from what has already been described. One is a definite exostosis arising directly from the periosteum or osteum, that is, having at its base the normal cortex of the bone. These occur most commonly on the diaphysis, anywhere between the ends of the bone. In appearance they are not different from mechanical exostosis seen in many individuals. The other is rather a nodular swelling of the periosteum, organized to a certain extent, but to be differentiated from the cortex and also having as its base the

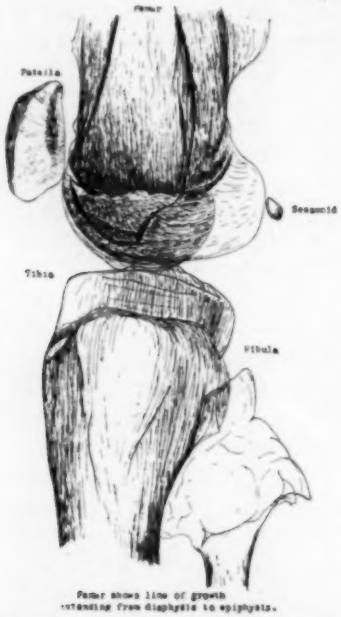


Fig. 26.—The ends of the bones are enormously enlarged, irregular in shape and outline, with curiously shaped growths. They originate in the diaphysis but encroach on the epiphysis.

cortex. The surface is not broken, is smooth, with an elevation of a centimeter or more, and three or more centimeters in diameter. They also occur on the diaphysis, frequently near the middle and on otherwise unaffected bone. They occur frequently, if not always, after an injury, may disappear gradually, and, on the other hand, may develop rapidly. The history in two of these cases gives proof of this, and in one case this was observed. These nodules may become completely ossified. It is suggested that this type of exostosis and these nodules have a common cause, for they are constantly associated. It further-

more suggests that the bone itself is sensitive to injury and sets up an inflammation, reacting in this manner.

There is no evidence from the roentgenograms to show that these growths are anything but benign. No evidence is obtained that any

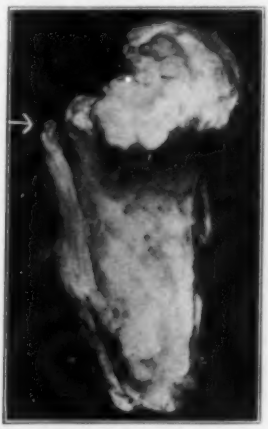


Fig. 27.—Pseudo-epiphysis produced by the process of exostosis, with cauliflowerlike cartilaginous surface and with processes for the insertion of muscles. × 1.

Fig. 28.—Longitudinal section of pseudo-epiphysis showing solid bone throughout, with an irregular cross line at the neck and spongy substance at the cartilaginous surface. There is no medullary canal. × 1.

degenerative changes occurred. These growths develop slowly in some cases and rapidly in others. In one case (G) the growth, exostosis, was removed. A drawing of this is shown (Figs. 27 and 28), and the pathologic report is also included in this paper.

In many instances symmetrical changes are seen, that is, in distribution. But since the disease affects the epiphysis, ends of the diaphysis and diaphysis, and is a general skeletal systemic disease, some symmetry in distribution is to be expected. The growths vary; the position of the growths vary, their size, structure and development varies, and in this respect they are not symmetrical. In examining some of the growths in detail, one or two interesting points are brought out. In the case of G. a very typical growth shows a cauliflowerlike end 2.5 by 3 cm. in size. The growth is about 10 cm. in total length and is situated 13 cm. from the lower end of the femur. The end is made up of numerous, small, semicircular areas of transparency much like a honey comb (Figs. 29, 30 and 31). The surface outline is no greater in density than the internal structure, indicating cartilaginous nature and no peripheral bone salts deposit. In the case of B. a similar type of growth is seen occurring on the inside of the shaft of the right femur. Here the growth, however, shows calcification with differentiation between cortex and canal. The peripheral outline is denser than the rest of the bone growth and its outline smooth. Comparing this growth with that of G. there is a suggestion that differentiation in the growth occurs only when general growth has ceased. In the case of G. we are dealing with an individual who has not reached maturity, as judged from the normal line of ossification, in the case of B. with an individual who has. It is further suggested, that the processes are most active and form a part of general bone growths in youth, in no way controlled or restricted as occurs in normal bone growth, maturity alone restricting growth.

In the growth from patient G. a fracture through the shaft of the growth occurred, 3 cm. from its base. No symptoms were present.

In the general roentgenographic description of the bones it will be noticed that the increased transparency and the penciling is a prevailing change. The question arises, therefore, whether these growths affect the structure and strength of the bones. Attention has been drawn to the early inhibition of growth, of bowing and general mechanical changes. On close examination of some of the bones that show bowing, it is found that this does not occur in the region of an unaffected shaft but in both the upper and lower ends of the diaphysis which, as already described, show bone changes. Do the growths or the general processes which give rise to them affect the bone? This I believe to be the case, and if the metabolic tables are studied the question will arise whether the increased elimination of salts can possibly come from the growths alone or are at the expense of the bones themselves. The metabolic disturbances and the growth processes have, then, a relation to one another. On the one hand, we have restricted bone growth, and on the other, excessive, uncontrolled bone growths

in various forms. From this standpoint it is assumed, then, that metabolism was disturbed or imperfect very early in life, perhaps in utero. If attention is also drawn to the fact that these bone disturbances cease after maturity has been reached, the above assumption is even more acceptable (see results of metabolic studies).

Rickets is an analogous condition in the long bones, except that no growths occur and the hereditary factor is absent. It is a disease due to metabolic disturbances and results in very definite bone changes affecting growth.

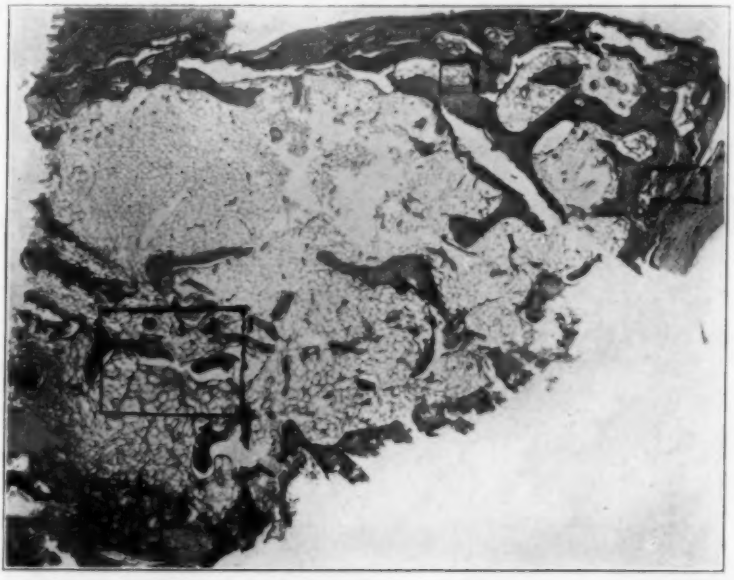


Fig. 29.—Cross section of pseudo-epiphysis. The squared areas are enlarged in Figures 30 to 33. × 15.

In multiple cartilaginous exostosis there is no association with any other disease so far as is known, and the only complications are those which arise or occur in the growths themselves; degenerative changes, malignancy or fractures and these are infrequent. Mechanical inconveniences due to the growths are not complications.

As has been pointed out by numerous investigators, the male is affected most commonly; the ratio is more or less three to one.

The last question is one of heredity. A careful study of the literature leaves no other conclusion but that it is an hereditary disease. From earliest times to the present day the literature on the subject presents very convincing evidence that hereditary factors play a part

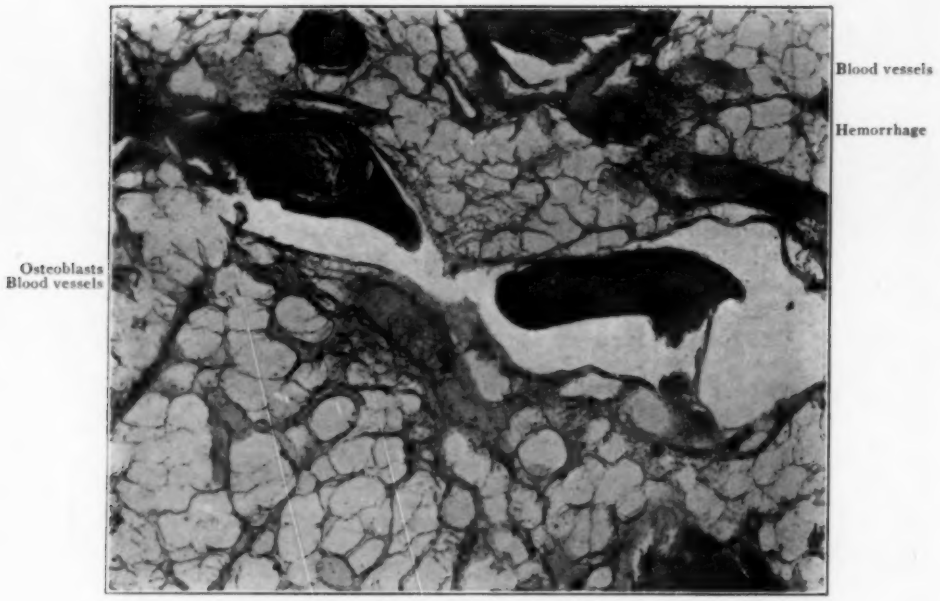


Fig. 30.—Bony spiculae surrounded by osteoplastic connective tissue. × 70.

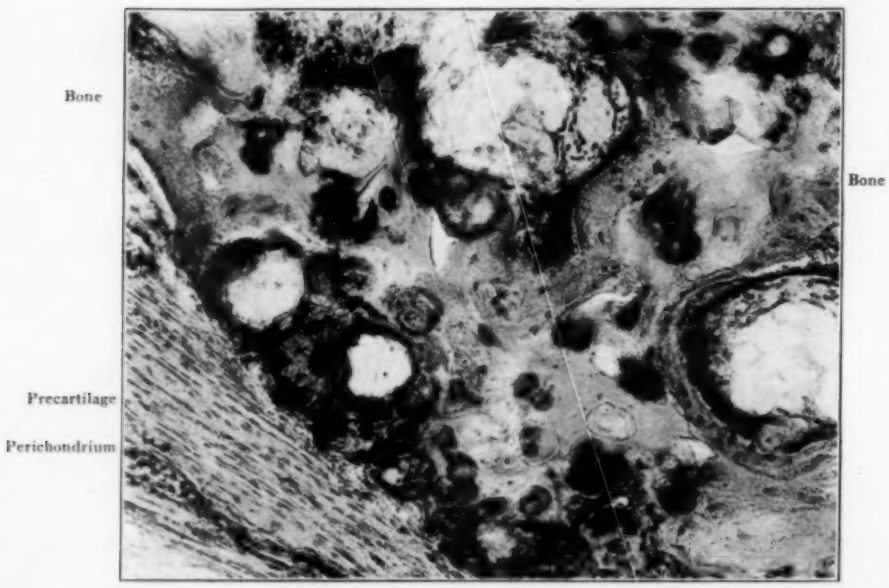


Fig. 31.—Precartilage with perichondrium in transition to bone. × 150.

It is hardly convincing that, because no evidence of the disease appears in the ancestors of a given patient, that hereditary factors should be ruled out, for it presumes that the disease is, therefore, one of remarkable individual selection. This paper, however, does not pretend to enter the discussion of the hereditary factors. That is a study by itself.

CALCIUM AND MAGNESIUM METABOLISM

Two patients, G. and H., were studied. These patients were placed on a known diet low in calcium and magnesium for a definite period. Either calcium or magnesium was then added for a second period. Calcium intake was increased by the administration of milk. Magnesium was given in the form of citrate. By the procedure outlined it is apparent that the system was given a distinct task to perform. The manner in which this task was accomplished by the diseased system was checked up by comparison with normal subjects maintained under similar experimental conditions. Of these two cases, one had advanced to the stage where the abnormal processes had become stabilized (H.). The other case (G.) represented the active, less advanced stage of the disease.

RESULTS OF EXPERIMENT

From a consideration of the study of multiple exostosis it may be concluded that in the stabilized stage of this disease calcium exchange differs little from that of a normal individual whether the abnormal subject is maintained on a calcium poor or a calcium rich diet.

In the progressive stage of the disease calcium metabolism is markedly different from the normal in that calcium is lost from the body in relatively large amounts when the subject is maintained on a calcium poor diet. This excessive elimination of calcium is excreted by both the urine and feces in a normal ratio. When placed on a calcium rich diet, calcium is retained in the body to an extent not widely different from that in normal subjects. A resumption of a calcium poor diet again induces excessive calcium elimination.

In the stabilized stage of multiple exostoses, magnesium excretion is from two to three times as great as the intake, whether the subject is maintained on a diet poor or rich in magnesium. In the progressive stage of the disease, the general type of magnesium excretion resembles that of the stabilized stage but the degree of elimination is not so marked. Magnesium added to the diet in the stabilized stage results in the prompt excretion of the magnesium. The same test applied to the progressive stage gives evidence of the retention of some magnesium. The degree of retention, however, is much less than that shown by normal individuals.

Absorption of both calcium and magnesium in multiple exostosis is not inferior to that of normal subjects.

The facts enumerated suggest that in the early stages of this proliferative type of bone disease under discussion a check may perhaps be given to the progress of the disease by proper dietary procedure. (A complete report of the calcium and magnesium metabolism will be published in the *Journal of Experimental Medicine*.)

PATHOLOGY

It seems to be the general opinion that the process of increased bone formation in these cases is derived from collections of cartilage cells during the transitional period from cartilage to bone, but this is of secondary importance. There is evidence of vicious cartilage growth, with very slow ossification, as is shown by the character, enlargement, fusion, malformation and bowing of the ends of the long bones. If, however, the growths are developed only from the cartilaginous forming bone, it is difficult to account for the origin of the growths on the other bones, such as on the skull and face. It is true, that these growths are more rare, but that does not change the theory as to the origin. Growths on the shaft of the bone are not different from those occurring near the ends and their origin may be the same. Some of these growths appear to have their origin from the periosteum, for as far as can be determined, the cortex of the shaft is intact; these must have occurred a considerable time after the formation of the bone. Other growths which cannot be differentiated from the bone itself must have had their origin during or before the formation of the bone.

The growths are variously described, owing to the fact that the examinations were made at different ages and developmental periods. A growth may be developed so completely that it cannot be differentiated from the normal bone having periosteum, cortex and medullary canal. In the stages where ossification has not yet taken place, these growths, some with large collections of nonregulated cartilage cells embedded in a spongy, more or less fibrous matrix, may have a membrane or periosteum surrounding them. Later the central spongy tissue may become more compact and bone cells may be found in or near the periphery. Frequently the periphery of the growth is solid, compact cartilage and areas of calcium and internally cellular tissue are sometimes seen. Calcification in irregular areas occurs while the cartilaginous growth is still active. Differentiation apparently only occurs when active cartilaginous growth has ceased.

An examination of the growth removed from the femur in case G. demonstrated the following:

There is a thick layer of dense connective tissue which represents the periosteum (Figs. 32 and 33). It contains numerous dilated and congested blood vessels. On its internal surface groups of large, elongated cells can be seen. They have large vesicular nuclei and show a regular placed arrangement in one row, resembling epithelial cells. These osteoblasts cover the surface of the thick layer of compact bone and cartilaginous tissue, which forms the periphery of the nodule. From the periphery similar trabeculae of bony tissue can be followed also into the interior. Near the surface smaller or larger cavities with walls of compact bone can be seen; deep in the interior,

Fig. 32.—Periosteum and bone including precartilage. × 150.

however, only bony spiculae are found surrounded sometimes with dilated and engorged blood vessels. The interior mainly is made up of loose connective tissue (mostly fat) which is richly supplied by a network of blood vessels.

These are dilated and form rich anastomosis. Hemorrhages which may be the result of traumatism are quite numerous, and free blood may fill sinuses in the loose connective tissue. Sometimes only narrow strands of connective tissue, covered with a row of osteoblasts, separate the blood vessels from the spiculae. The bone tissue in the periphery as well as in the interior (trabeculae, spiculae) is compact in structure

and shows no regular arrangement in Haversian system. The Howship cavities of absorption are also missing. The surfaces are smooth, and there is no medullary canal with bone marrow. Here and there, however, a few lymphocytes are seen. Scattered on the surface there are numerous imperfectly developed cartilaginous nodules, which form imperceptible transitions to the bony tissue. These nodules vary in size and often only a small cartilaginous area can be seen included in the bony tissue. The cartilage cells are irregular in shape and size. They are in large part closely packed, giving the typical picture of precartilaginous tissue. This is surrounded with perichondrium, which is

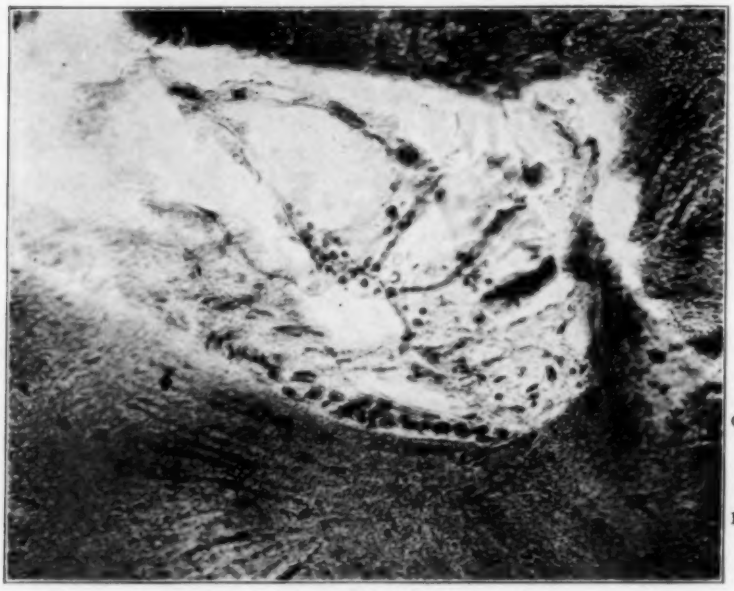


Fig. 33.—Bone with the osteoplastic connective tissue. × 150.

sometimes continuous with the periosteum. (A complete pathologic study is being made and will be reported in the near future by Dr. N. M. Alter.)

In a great deal of the literature apparently no difference has been made between the multiple cartilaginous exostosis and mechanical or traumatic exostosis. In the older reports of cases this has made it exceedingly difficult to tabulate and analyze the results. A good deal of the conflict of opinion regarding exostosis is because of this failure to differentiate the two conditions. The frequency of the occuurrence of malignancy in these growths cannot be determined for this very reason.

ANALYSIS OF REPORTED CASES

In a detailed analysis and classification of sixty-six reported cases, information was obtained which supports certain suggestions and opinions of the present paper.

Age Incidence.—Of sixty-six cases, fourteen occurred between 1 and 10 years of age; seven between 10 and 15 years; eleven between 15 and 20 years; nine between 20 and 25 years; ten between 25 and 30 years; and fourteen over 30 years of age.

Sex.—Of sixty-three cases, there were forty-seven males and sixteen females.

Hereditary History.—In thirty-three cases, a positive history of heredity was obtained in thirteen, the disease having occurred in some member or members of the patients' families. In one case, eight members were affected, and in several other cases many members were similarly affected.

Beginning of Growth.—In one case the growths were noticed at birth, in twelve cases they were noticed between birth and 5 years of age. Between the age of 5 and 10 years, there were seven cases; between 10 and 15 years, four cases; between 15 and 20 years, two cases, and in one case growths were noticed after 20 years of age. The remaining cases gave no definite information.

Cessation of Growth.—Only twelve patients gave information in this respect. In six cases growth ceased after operation, and in one it progressed; in one case it ceased at puberty; in one case after 11 months of age, and in three cases at 17, 22 and 25 years, respectively.

Order of Frequency.—The femur was affected in 43 cases; tibia in 35 cases; humerus in 29 cases; fibula in 27 cases; radius in 25 cases; ulna in 24 cases; phalanges in 20 cases; ribs in 19 cases; scapula in 17 cases; pelvic bones in 13 cases; clavicle and metacarpals in 12 cases each; metatarsal bones in 6 cases; skull bones in 6 cases; knee in 4 cases; the spine and tarsal bones in 2 cases each and the sternum in one case.

Position of Growth.—Femur: Diaphysis was affected most frequently, condyles next, and then the epiphysis and trochanters. Tibia: The upper extremity showed more frequent changes, then the lower end of the shaft, epiphysis and near epiphysis. Fibula: This bone showed changes in approximately the same order of frequency as the tibia. Humerus: In the majority of cases the shaft was affected, and in only one case was the epiphysis attacked. Growths near the epiphysis were the second most common occurrence. Radius and ulna: The carpal extremity in both these bones showed changes most often, and the diaphysis and epiphysis with equal frequency. Phalanges: There was no predominating change in any of the phalanges either in posi-

tion or in any particular phalanx. The hands were more affected than the feet. Ribs: The middle of the ribs were affected mostly, particularly the third, fifth, sixth, eighth and tenth ribs. Scapula: The vertebral border and the spine were more frequently mentioned than other parts of the bone. Pelvis: The ilium and especially the crest were the parts most frequently affected. Clavicle: The acromial end and the near acromial end were more often affected than the sternal end or the middle. Metacarpals: Both epiphysis and diaphysis were attacked, otherwise no significant change predominated in any one part. Metatarsals: Both epiphysis and diaphysis. Skull bones: The face bones were affected in three cases and the frontal, temporal and occipital areas in one case each.

RÉSUMÉ

Multiple cartilaginous exostosis is a disease with the following distinctions:

1. It presents hereditary factors.
2. It is a disease with definite, well defined metabolic disturbances.
3. There is no evidence that infection plays a part.
4. It begins in early life, and probably before birth.
5. It occurs more in males than females.
6. It gives rise to obvious bone changes, inhibitory and stimulatory and at an age not yet determined.
7. The long bones and flat bones are affected.
8. Both epiphysis and diaphysis are involved.
9. Malformation and deformities occur at an age not yet determined, due to arrest in growth of the skeleton and to bone growths arising at such points as to interfere with the normal growth and direction of the bones.

BIBLIOGRAPHY

Ashhurst, A. P. C.: Multiple Cartilaginous Exostoses. (Hereditary Deforming Chondrodysplasia), Ann. Surg. **68**:167, 1916.

Barlow, John: Patient with Sarcoma of the Lower End of Femur and Multiple Exostoses, Glasgow M. J., 1895.

Bec and Hadengue: Echondromes Multiples de la Main, J. de Radiol. et d'Electrol. **3**:63, 1918.

Bernard, Léon: Exostoses Ostéogéniques, Maladies des Os, p. 564.

Bessel-Hagen, F.: Ueber Knochen und Gelenkanomalien insbesonders bei partiellen Riesenwuchs und bei multiplen cartilaginären Exostosen, Arch. f. klin. Chir. **41**:420, 505, 749, 1891.

Bloodgood, J. C.: Benign Bone Cysts, Ostitis Fibrosa, Giant Cell Sarcoma and Bone Aneurysm of the Long Pipe Bones, Tr. Am. Surg. A. **28**:116, 1910.

Boggs, T. R.: Multiple Congenital Osteochondromas with Degeneration of Cranial Nerves and Muscular Dystrophy; Report of a Case, Tr. A. Am. Phys. **28**:248, 1913.

Borchardt: Demonstration eines Osteochondrosarcoms der Epiphyse des Humerus, Berl. klin. Wchnschr. **40**:575, 1903.

Boyer: Traité des Maladies Chirurgicales **3**:598.

Braune: These (de) Halle, 1882.

Byers, W. G.: Case of Exostosis Bursata, Montreal M. J. **24**:967, 1895.

Carman, R. D., and Fisher, A. O.: Multiple Congenital Osteochondromata, Ann. Surg. **61**:142, 1915.

Cheever, D. W.: Exostosis of Facial Bones, Boston M. & S. J. **115**: 1886.

Clarke, W. B.: A Case of Multiple Exostosis, Tr. Med. Soc. London **15**: 453, 1891.

Cowie, David M.: Hereditary Multiple Exostoses, Am. J. Obst. **76**:535, 1917.

Cox, Robert: Notes on a Case of Multiple Exostoses with Hereditary History, Lancet, London, **2**:701, 1915.

Crawford, D. G.: Case of Multiple Exostoses, Indian M. Gaz. **44**:340, 1909.

Curtillet, J.: Quatre Cas d'Exostoses Ostéogéniques Multiples, Héréditaires et Familiales: due Rôle Probable des Toxi-infections dans la Production des Exostoses Ostéogéniques, Rev. d'orthop. **3**:193, 1912.

Davis, G. G.: Multiple Cancellous Exostoses, Am. J. Orthop. Surg. **3**: 234, 1905.

Delfino, E. A.: Contribution à l'Etude des Exostoses Multiples, Arch. d'Electricité méd. et de Physiothérap. **25**:423, 1917.

Drescher, Adolph: Zur Casuistik der Hereditären Multiplen Exostosen, These, Giessen., 1889.

Edberg, E.: Sur les Rapports Existant Entre le Développement des Exostoses des Cartilages de Conjugaison et Certain Alterations de la Glande Thyroide, Lyon Méd. **125**:24, 1916; Nord. med Ark. **29**: 1915.

Ehrenfried, Albert: Multiple Cartilaginous Exostoses; Hereditary Deforming Chondrodysplasia, J. A. M. A. **64**:1642 (May 20) 1915. Hereditary Deforming Chondrodysplasia; Multiple Cartilaginous Exostoses, J. A. M. A. **68**:502 (Feb. 10) 1917. Hereditary Deforming Chondrodysplasia: More Cases, Am. J. Orthop. Surg. **15**:463, 1917.

Gibney, V. P.: Hereditary Multiple Exostosis; Four Cases with Remarks, Am. J. M. Sc. **72**:73, 1876.

Gill, A. Bruce: Multiple Enchondromata of Hand, Ann. Surg. **66**:623, 1917.

Hamann, C. A.: Multiple Cartilaginous Exostoses (Hereditary Deforming Chondrodysplasia), Ann. Surg. **63**:167, 1916.

Heath, P. Maynard: Multiple Exostoses, Proc. Roy. Soc. Med. **4**:103, 1910.

Heymann, R.: Ein Beitrag zur Heredität Seltenerer Geschwulstformen Multiple Cartilaginäre Exostosen, Arch. f. Pathol. Anat. u. Physiol. **104**:145, 1886.

Huber, K.: Ein Seltenerer Fall von Multiplen Cartilaginären Exostosen, Arch. f. Pathol. Anat. u. Physiol. **88**:256, 1882.

Jouffray: Exostoses Ostéogéniques Multiples, Lyon Méd. **106**:263, 1906.

Krieble, Vernon K., and Bergeim, Olaf: Study of the Metabolism in Multiple Exostoses, J. Biol. Chem. **37**:179, 1919.

Läwen, A.: Ueber die Beziehungen der Enchondrome zu den Multiplen Cartilaginären Exostosen, Deutsch. Ztschr. f. Chir. **75**:14, 1904.

Lenormand C., and Lecène, P.: Sur l'Association des Exostoses Ostéogéniques et du Chondrome des Os, Rev. d'orthop. **7**:203, 1906.

Lett, Hugh: Multiple Cancellous Osteomata, Proc. Roy. Soc. Med. **2**:191, 1909.

Maclean, E. J.: Multiple Cancellous Exostoses, Brit. M. Chir. J. **8**:217, 1890.

McKail, J.: Case of Multiple Exostoses, Arch. Radiol & Electrother. **21**: 286, 1917.

Margery: Note sur une Différence Considérable de Longueur des Deux Membres Inférieurs observée chez un jeune homme de 21 ans, etc.; Enchondromes Multiples des Extrémities, Gaz. Hebdom. de méd. et Chir. **29**:246, 1892.

Marshall, H. W.: A Case of Multiple Cartilaginous Exostoses, Am. J. Orthop. Surg. **14**:346, 1916.

Mery, M.: Description d'une Exostose Monstreuse, Hist. Acad. Roy. d. Sc., 1706, Par. 1707, Mém. 245-248.

Meyer, A. W.: Unusual Exostoses on Two Humeri and a Femur, etc., J. Anat. & Physiol. **48**:138, 1913.

Montgomery, C. M.: Multiple Cartilaginous Exostoses. (Hereditary Deforming Chondrodysplasia.) A Report of Five Cases in Three Generations, Internat. Clin., Phila. **26**:140, 1916.

Moschcowitz, A. V.: Multiple Cartilaginous Exostoses Ann. Surg. **68**:749, 1916.

Mosenthin, H.: Seltenere Komplikayionen der Multiplen Kartilaginären Exostosen, Deutsch. Ztschr. f. Chir. **128**:241, 1914.

Nasse, D.: Ueber Multiple Cartilaginäre Exostosen und Multiplen Enchondroma, Samml. klin. Vorträge, No. 124, 1895 (Chir. No. 34, p. 209).

Nehrkorn, A.: Multiple Enchondrome der Knochen in Verbindung mit Multiplen Subcutanen Teleangiektasien, Beitr. z. klin. Chir. **22**:800, 1898.

Niederle: (Cited by A. Lenormand and P. Lecène, Rev. d'orthop. **7**:203, 1906.)

O'Ferrall, J. T.: Multiple Cartilaginous Exostoses; Report of Cases, New Orleans M. & S. J. **69**:808, 1917.

O'Neil, J. S.: A Case of Exostosis, Indian Med. Gaz. **48**:284, 1913.

Opie, E. L., and Allison, N.: Hypertrophic Chondrodysplasia in Infancy and Adolescence; Progressive Anomaly of Osteogenesis, J. Med. Res. **36**:277, 1917.

Pels-Leusden, F.: Klinische und Rdiologische Studien über Exostosis Cartilaginea Multiplex, Ztschr. f. Chir. **86**:434, 1907.

Parry, L. A.: Multiple Exostoses, Brit. M. J. **2**:131, 1905.

Percy, Nelson M.: Multiple Chondro-Osteoma, Surg., Gynec. and Obst. **20**: 619, 1915.

Perrin, M.: Exostoses Ostéogéniques Multiples Accompagnées d'Arrêts de Développement et de Déformations du Squelette, Rev. d'orthop. **5**:53, 1914.

Rendu and Fouilloux: Volumineux Chondromes des deux Mains, Exostoses, Troubles de Développement du Squelette des Membres Chez une Fille de 10 Ans et Demi, Lyon Méd. **122**:409, 1914.

Rendu, A., and Levy, P.: Exostoses Ostéogéniques Multiples Accompagnées d'Arrêts de Développement et de Déformations du Squelette, Lyon Chir. **12**: 164, 1914.

Richter: These. Jena, 1894 (Cited by A. Lenormand and P. Lecène, Rev. d'orthop. **7**:203, 1906).

Rutherford: A Boy with Multiple Exostoses, Glasgow M. J. **43**:451, 1895. Specimen of Exostosis of Ungual Phalanx of the Great Toe, Ibid.

Sonnenschein: These (de) Berlin, 1873 (Cited by A. Lenormand and P Lecène, etc.)

Sourdat, P.: Complications Rares des Exostoses Ostéogéniques, Arch. Prov. de Chir. **21**:168, 1912.

Spriggs, E. G.: Case of Multiple Exostosis, Proc. Royal Soc. Med. **2**: 202, 1909.

Strachan, Henry: Bony Overgrowths or Exostoses in the West Indian Negro, Brit. M. J. **1**:189, 1894.

Trendelenburg, F.: Dupuytren Exostosis of the Big Toe, Internat. Clin., Phila., **12**:215, 1898.

Turner, P.: Case of Multiple Exostoses, Proc. Roy. Soc. Med., Lond. **7**: 107, 1913.

Virchow: Demonstration einiger Präparate zur Pathogenesis der Enchondrome, Berl. klin. Wchnschr. **1**:94, 1864. Enchondroma Malignum mit Multiplen Knorpligen Exostosen, Charité Ann. **5**:736, 1878. (Cited by A. Lenormand and P. Lecène, Rev. d'orthop. **7**:203, 1906.)

Von Bergman: Freie Vereinig. d. Chirurg. Berlins, March 13, 1905. (Cited by A. Lenormand and P. Lecène, Rev. d'orthop. **7**:203, 1906.)

Von Haberer, Hans: Ein Fall Von Multiplen Enchondromen und Exostosen, Arch. f. klin. Chir. **89**:782, 1909.

Von Kryger: Multiplen Knochen und Knorpelgeschwülste, Arch. f. klin. Chir. **57**:859, 1898.

Von Recklinghausen, F.: Ein Fall von Multiplen Exostosen, Arch. f. Pathol. Anat. u. Physiol. **35**:203, 1866.

Weber, Otto: Zur Geschichte des Enchondroms Namentlich in Bezug auf dessen Hereditäres Vorkommen und Secundäre verbreitung in Inneren Organen durch Embolie, Virchow's Arch. f. Pathol. Anat. u. Physiol. **35**:501, 1866.

TOXIC JAUNDICE IN PATIENTS UNDER ANTI-SYPHILITIC TREATMENT

A STUDY OF THE CHEMICAL ANALYSES OF THE BLOOD AND URINE, AND OBSERVATIONS ON THE EFFECT OF EXERCISE AND DIET IN THE TREATMENT OF SYPHILIS *

CAMERON V. BAILEY, M.D., AND ANGUS MacKAY, M.B.
WOODSTOCK, ONTARIO, CANADA

The treatment of syphilis by injections of arsenobenzol derivatives is, at times, accompanied by more or less grave signs of intoxication. Of these, three distinct types seem to arise. In the first type, symptoms of general malaise shortly follow the administration of the drug and, as a rule, pass off within twenty-four hours. In the second and third types, toxic symptoms may be delayed and not appear until several months after the cessation of treatment. The most pronounced symptoms are associated with the skin or liver.[1] The skin lesion usually develops in the course of the treatment as a maculopapular eruption with considerable thickening. This rapidly becomes generalized. Desquamation is profuse, leaving a thickened, cyanosed and frequently pigmented surface. Pustulation is common. The patient becomes debilitated and has a slight fever. The liver and spleen are frequently enlarged. The urine shows a trace of protein and bile pigment. Patients whose liver symptoms predominate may pass several weeks in apparently good health following their course of treatment, and then come under observation with general malaise and jaundice. The latter, at first slight, becomes more pronounced. The liver, and frequently the spleen, becomes enlarged and tender. The blood pressure, pulse and temperature are usually low. Symptoms as in acute yellow atrophy of the liver may supervene,[2] or the patient may slowly convalesce.

A jaundice of the above type, occurring during the secondary stage of syphilis, has frequently been described. Rolleston,[3] reviewing the literature on this subject, points out that this condition has frequently arisen in untreated cases and is not necessarily due to medication. Such cases improve under antisyphilitic treatment. The cases

---

* From the Laboratory of Pathology, Ontario Military (No. 16 Canadian General) Hospital, Orpington, Kent.

1. Harrison, L. W.: Quart. J. Med. **10**:291 (July) 1917.
2. Willcox, W. H.: Lancet **1**:869 (May 24) 1919.
3. Rolleston, Sir Humphry: Diseases of the Liver, Gallbladder and Bile Ducts, London, 1912.

recognized as arsphenamin poisoning, on the other hand, are greatly aggravated by treatment. Untreated cases, in which jaundice and its associated signs occur coincidently with the syphilitic skin lesions, bear a marked resemblance to many of the arsphenamin cases in which a mild jaundice is associated with severe dermatitis. It is possible that the arsenic in these cases simply accentuates a reaction which, to a mild degree, is ordinarily present in syphilis.

PREVENTIVE MEASURES

Unfortunately, the susceptible patients cannot be recognized, and, in spite of all precautions, the first intimation of trouble is the onset of the severe toxic symptoms. Of precautionary measures in administering treatment, the examination of the urine for signs of nephritis is recommended.[4] Few of the cases, however, show such signs, and, on the whole, the kidneys are impaired but slightly, if at all. Testing the urine for bile pigment is equally of little use as the warning does not come in time. Of greater value in determining the state of jaundice is the test for bile pigment in the blood serum or plasma, and for this Gmelin's test is quite satisfactory.[5] It is generally conceded that the development of any untoward symptom in the course of treatment should be considered carefully before further injections are given. The size and frequency of the dose have both been reduced greatly; Willcox and Webster[6] recommend 0.3 gm. of arsphenamin or similar preparations (which is half the original dose) and the interval between doses to be two or three weeks. In using full doses (0.6 gm.), they recommend an interval of four weeks between injections. These intervals permit a complete elimination of the arsenic before a succeeding dose is given. Harrison,[1] referring to the cumulative effect of these remedies, states that "patients who have shown the most toxic effects have, in the majority of instances, done so after a number of doses have been administered." In a number of his cases, in which the intervals between treatments was sufficiently long to permit the excretion of all the arsenic, toxic symptoms developed after several treatments. He suggests that each succeeding dose contributes its quota to the damage, and finally definite toxic symptoms are precipitated by a final dose.

4. See Reference 23.

5. Considering that bilirubin is frequently found in the plasma of apparently healthy individuals, its determination by chemical methods is of little diagnostic value. Its repeated quantitative estimation in a particular case is an aid in following the course of the illness. The quantitative method described by Blankenhorn is of value in this respect. Blankenhorn, M. A.: Tr. A. Am. Phys., 1917.

6. Willcox, W. H., and Webster, J.: Brit, M. J. **1**:473 (April 1) 1916.

Conditions similar to acute yellow atrophy of the liver have frequently been observed following combined mercurial and arsenical treatment,[7] and it is of interest to recall that such symptoms have followed mercury alone.[8] In selecting the dose of arsenic in these cases, the added toxic factor of the mercury must be considered. As a preventive of immediate toxic symptoms, Westrope[9] reports favorable results from the use of a milk diet for twenty-four hours before the injection of the drug.

EXAMINATION OF CASES

An opportunity was afforded of making a chemical examination of the blood and urine in twenty-five cases of toxic jaundice following antisyphilitic treatment, and in fifteen cases convalescent or recovered from other illnesses. At the time of the examinations, the patients had shown toxic symptoms for periods ranging from 16 to 136 days; the majority were still slightly debilitated, others had apparently recovered. Six had bile pigment in the urine. None of the patients had proteinuria or other sign of nephritis, although in some cases the clinical history indicated that such symptoms had been present in the course of the illness. The antisyphilitic treatment in these cases consisted of an intravenous injection of novarsenobenzol (Billon) and a synchronous intramuscular injection of mercury, the doses being repeated at intervals of seven days.

CASE HISTORIES

Case 1.—Male, aged 55; weight 116 pounds; no history of previous illness or infection.

October, 1918: Weakness, precordial pain and palpitation.

June 27, 1919: General weakness; liver 5 inches below costal margin; spleen, enlarged; blood pressure, 122/72; temperature, normal; hemoglobin, 53 per cent.; red cells, 3,736,000; Wassermann, +++.

Diagnosis.—Syphilitic hepatitis.

Case 2.—Male, aged 23; weight 158 pounds. March 7, 1919: Exposure; sore discovered on penis the following day. Received novarsenobillon, 1.05 gm. and mercury, 0.128 gm., in two treatments with an interval of seven days. Following the second treatment he developed "swelling of the face" and nausea. He later became jaundiced.

April 4: Urine contained a trace of protein and bile pigment.

May 11: Well-marked icterus; liver at costal margin; spleen, not palpable; blood pressure, 130/80.

June 13: No arsenic found in urine seventy-four days after last treatment.

June 20: Urine constantly contained bile pigment, at times a trace of protein and on one examination tyrosin. He has never given a positive Wassermann reaction.

June 27: Chemical blood analysis. Clinical findings negative.

---

7. Severin: Ztschr. klin. Med. **76**:138, 1912; Bedig: Münch. med. Wchnschr. **62**:1140, 1915.
8. Tileston, W.: Boston M. & S. J. **158**:510, 1908.
9. Westrope: Brit. M. J. **2**:456, 1916.

CASE 3.—Male, aged 24; weight, 155 pounds. Jan. 25, 1919: Chancre.

March 6: Combined treatment instituted; received novarsenobillon, 4.05 gm., and mercury, 0.45 gm., in seven treatments with seven day intervals. Following the fifth treatment, nausea and jaundice developed.

May 11: Slight icterus; liver 1 inch below costal margin; urine showed a trace of protein, no bile pigment, leucin, tyrosin of bile salts.

June 17: No arsenic found in urine fifty-two days after last treatment.

June 27: Chemical blood analysis. Clinical findings, aside from slight debility, were negative.

CASE 4.—Male, aged 34; weight, 146 pounds. Dec. 26, 1918: Chancre.

March 30, 1919: Had received novarsenobillon, 4.05 gm., and mercury, 0.45 gm., in seven treatments with seven day intervals. He became ill and jaundiced after the last injections.

May 11: Marked jaundice, liver, 1.5 inch below costal margin; spleen, slightly enlarged; blood pressure, 128/86. Bile pigment in urine, no protein, leucin or tyrosin.

June 13: No arsenic found in urine seventy-one days after last injection.

June 27: Chemical blood analysis. Clinical findings, aside from slight debility, were negative.

CASE 5.—Male, aged 24; weight, 134 pounds. Jan. 1, 1919: Chancre.

March 8, 1919: Had received novarsenobillon, 4.65 gm., and mercury, 0.518 gm., in eight treatments with intervals of seven days.

May 14: Jaundice developed.

May 20: Slightly jaundiced; pupils unequal, liver tender and 1½ inch below costal margin; spleen not palpable; blood pressure, 128/80. Urine contains a trace of bile pigment; no protein.

June 13: No arsenic found in urine ninety-three days after last injection.

June 27: Chemical blood analysis. Clinical findings, aside from slight debility, were negative.

CASE 6.—Male, aged 24; weight, 150 pounds. July, 1917: Received novarsenobillon, 4.05 gm., and mercury, 0.45 gm., in seven treatments with intervals of seven days. Following this he was somewhat debilitated. These treatments were repeated in October, 1918, and again in January, 1919. In May, 1919, he had an abscess of the left buttock associated with severe generalized furunculosis and great weakness. Liver was tender and 1½ inch below costal margin. Spleen, palpable. Wassermann, negative. Urine, contained a trace of bile pigment; no protein. Blood pressure, 110/67.

June 17: No arsenic found in urine 117 [illegible] after last injection.

July 1: Chemical blood analysis. [illegible] healed. Debilitated.

CASE 7.—Male, aged 20; weight 155 pou[illegible] 20 1919: Chancre.

May 8, 1919: Had received novarsenobil[illegible] n., and mercury, 0.388 gm., in six treatments with intervals of seven days. Following the fourth injection he became febrile, and following the sixth injection he developed anorexia, jaundice and constipation; later, diarrhea.

May 24: Diarrhea; sclera jaundiced; skin clear; liver, palpable and tender; blood pressure, 100/65. Wassermann, negative.

June 13: Repeated urinalysis showed nothing abnormal. No arsenic found in urine thirty-six days after last injection.

July 1: Greatly improved. Chemical blood analysis.

CASE 8.—Male, aged 42; weight, 163 pounds. Dec. 5, 1918: Chancre.

Feb. 4, 1919: Had received novarsenobillon, 4.05 gm., and mercury, 0.45 gm., in seven treatments with intervals of seven days. Eleven days after the last injection, he developed pains in the chest and abdomen, weakness and constipation. Liver, 1½ inch below costal margin; spleen, palpable; Wassermann, negative; urinalysis, normal.

May 7. Apparently recovered. Given seven days' leave.

May 14: Returned markedly jaundiced, complaining of anorexia, weakness and a "distended feeling" in the liver region. Liver, 1½ inch below costal margin; tender. Urine contained a large amount of bile pigment; no protein. Wassermann, negative.

June 13: Urine free from bile pigment, protein, leucin, tyrosin and bile salts. No arsenic found in the urine 129 days after last injection.

July 1: Chemical blood analysis. Skin still discolored and he suffered from slight debility.

Case 9.—Male, aged 33; weight, 147 pounds. January, 1919: Chancre.

April 8, 1919: Had received novarsenobillon, 1.65 gm., and mercury, 0.194 gm., in three treatments with intervals of seven days. He became jaundiced after the last injection. Wassermann, negative.

May 22: Thin, distinctly jaundiced; liver, 1 inch below costal margin. Blood pressure, 108/70. Urine contained bile pigment; no protein.

June 13: No arsenic found in the urine sixty-seven days after the last injection. Aug. 1: Chemical blood analysis. Slightly debilitated.

Case 10.—Male, aged 31; weight, 137 pounds. Jan. 23, 1919: Chancre.

April 10, 1919: Had received novarsenobillon, 5.1 gm., and mercury, 0.58 gm., in nine treatments with intervals of seven days. April 23: Slight jaundice; gingivitis; ulceration of left cheek; weakness. Liver, tender, 2 inches below costal margin. Spleen, enlarged. Urinalysis, negative. No arsenic found in urine fifty-six days after last injection.

August 1: Chemical blood analysis. Jaundice had disappeared; liver and spleen were greatly reduced in size, and he had no complaints.

Case 11.—Male, aged 34; weight, 136 pounds. November, 1918: Chancre.

December-January, 1919: Received novarsenobillon, 4.05 gm., and mercury, 0.5 gm., in seven treatments with intervals of seven days.

April 15, 1919: Anorexia, nausea and jaundice.

May 1: Slight debility; moderately jaundiced; blood pressure, 112/78. No arsenic found in the urine 157 days after the last injection.

July 7: Chemical blood analysis. Liver had not decreased in size; otherwise his clinical findings were negative.

Case 12.—Male, aged 32; weight, 146 pounds. Ulcer on penis in 1911, for which he took pills for a period of eight weeks. Gassed in September, 1918. February, 1919: Urethritis; four weeks' treatment.

March 7, 1919: Received one injection of novarsenobillon, 0.45 gm.; furuncles appeared on legs and treatment was stopped.

April 26: Severe generalized dermatitis. Liver 2½ inches below costal margin. Spleen enlarged. Urine contained bile pigment. Wassermann, negative. No arsenic found in urine 125 days after last injection.

August 7: Chemical blood analysis. The liver and spleen had not decreased in size, the former, however, had lost its tenderness. The skin lesions had cleared up and he had no complaints.

Case 13.—Male, aged 29; weight, 144 pounds. December, 1915: Chancre.

February, 1916: Received three injections of arsphenamin.

June, 1916: Developed a second sore on penis. Received arsphenamin, 5.95 gm., and mercury, 0.64 gm., in ten treatments ending in September, 1917. Late in September, he developed nausea, vomiting, and general debility, necessitating six weeks hospital treatment.

January, 1919: Wassermann strongly positive. He received novarsenobillon, 2.25 gm., and mercury, 0.26 gm., in four treatments with intervals of seven days.

May 2: Headache, coated tongue, constipation and jaundice. Liver 1½ inch below costal margin. Spleen, not palpable. Blood pressure, 115/80. Urine contained a trace of protein and bile pigment.

June 13: Urine free from protein, bile pigment, leucin, tyrosin and bile salts. No arsenic was found in the urine ninety days after the last injection.

July 7: Chemical blood analysis. General condition had improved. Urine free from protein and bile pigment for two months. Liver and spleen still enlarged.

CASE 14.—Male, aged 23; weight, 138 pounds. October, 1918: Chancre. Received novarsenobillon, 4.65 gm., and mercury, 0.5 gm., in eight treatments with intervals of seven days, terminating Dec. 28, 1918.

April 28, 1919: Anorexia, followed in one week by pain in the liver region and jaundice.

May 10: Anorexia, constipation and jaundice. Liver, tender, 1⅓ inch below costal margin. Spleen, slightly enlarged. Blood pressure, 115/62. Urine contained bile pigment.

June 7: Jaundice disappeared. No arsenic found in the urine 180 days after last injection.

July 7: Chemical blood analysis. General condition had greatly improved; liver and spleen slightly decreased in size.

CASE 15.—Male, aged 22; weight, 135 pounds. February, 1916: Nephritis; ill eight months; recurrences in July, 1917, and May, 1918. February, 1919: Chancre.

March 4, 1919: Combined treatment instituted. Received novarsenobillon, 2.95 gm., and mercury, 0.324 gm., in five treatments with intervals of seven days. Nephritic symptoms developed.

May 14: Liver and spleen not palpable. Blood pressure, 125/80. No complaints. Urine contains a trace of bile pigment, protein and an occasional hyalin and granular cast.

August 7: Chemical blood analysis. Free from symptoms. Wassermann, negative.

CASE 16.—Male, aged 20; weight, 137 pounds. December, 1918: Chancre.

Feb. 14, 1919: Had received novarsenobillon, 4.05 gm., and mercury, 0.45 gm., in seven treatments with intervals of seven days.

May 10: Severe abdominal pains, followed by slight jaundice.

May 15: Slightly jaundiced; liver, palpable, not tender; spleen, not palpable. Blood pressure, 128/80. Urine contains a trace of protein and bile pigment; no bile salts or casts. Wassermann, negative. No arsenic found in urine eighty-eight days after last injection.

August 7: Chemical blood analysis. Jaundice had disappeared, liver was at costal margin, and he had no complaints.

CASE 17.—Male, aged 24. Jan. 1, 1919: Chancre.

April 4: Had received novarsenobillon, 4.05 gm., and mercury, 0.45 gm., in seven treatments with intervals of seven days. Following the third treatment, general malaise. Following the sixth treatment, severe dermatitis, which became greatly aggravated following the seventh and last treatment.

April 10: Marked gingivitis, stomatitis and purulent conjunctivitis. Skin brawny red with copper colored papules. Marked exfoliation. Blood pressure, 115/80. Liver not palpable. Urine contains bile pigment, protein, cholesterol, a few red blood cells and granular casts.

April 25: Liver 2 inches below costal margin. Spleen, enlarged. Dermatitis improving.

June 6: Urine contains bile salts; no bile pigment. August 13: Chemical blood analysis. General condition had greatly improved. The skin remained thickened and there was a slight desquamation. Liver and spleen had decreased in size. Wassermann, negative.

CASE 18.—Male, aged 23. Feb. 7, 1919: Chancre.

March 14, 1919: Had received novarsenobillon, 2.85 gm., and mercury, 0.32 gm., in five treatments with intervals of seven days. March 20: Developed a severe dermatitis. April 10: Skin thickened, purplish red, with a fine papular

eruption and marked scaly exfoliation. Moderate stomatitis and conjunctivitis. Liver and spleen not palpable. Blood pressure, 100/60. Urine contains bile pigment and salts; no leucin or tyrosin.

April 25: Liver 1 inch below costal margin. White blood cells, 17,200. Temperature, from 99 to 100 F.

May 9: Spleen, palpable.

July 13: Chemical blood analysis. Recovered from dermatitis. Liver and spleen still palpable. Wassermann, negative. Urine contained no arsenic ninety-one days after last injection.

CASE 19.—Male, aged 36. Received novarsenobillon, 4.05 gm., and mercury, 0.45 gm., in seven treatments with intervals of seven days, the course terminating in April, 1919. No immediate reaction. Wassermann, negative.

May 29, 1919: Returned from seven days' leave complaining of drowsiness, anorexia, nausea, clay colored stools and jaundice.

July 2: Markedly jaundiced; liver, palpable; tenderness over gallbladder. Urine contained bile pigment, a trace of protein and an occasional granular cast. No arsenic found in urine seventy-five days after last injection.

July 13: Chemical blood analysis. Clinical findings remained unchanged, excepting for the absence of protein and casts in the urine.

CASE 20.—Male, aged 21. Typhoid, 1910. Gonorrheal urethritis and prostatitis, February to May, 1919.

June 24, 1919: Weakness, nausea and jaundice. Liver and spleen palpable.

July 13: Chemical blood analysis. Jaundice and subjective symptoms had disappeared. Liver and spleen still palpable.

CASE 21.—Male, aged 27. Psoriasis. April 20, 1919: Chancre.

June 11, 1919: Had received novarsenobillon, 3.45 gm., mercury, 0.32 gm., in seven treatments with intervals of seven days. Following the third injection, chills, headache and muscular stiffness; following the fourth injection, a maculopapular eruption.

June 25: Marked generalized dermatitis with profuse desquamation. Liver, 1½ inch below costal margin. Wassermann, negative. No arsenic found in urine thirty-two days after last injection.

July 13: Chemical blood analysis. Clinical findings unchanged.

CASE 22.—Male, aged 37. Dec. 15, 1918: Chancre.

Jan. 29, 1919: Had received novarsenobillon, 3.45 gm., and mercury, 0.388 gm., in six treatments with intervals of seven days. Following the fifth treatment an eruption appeared on the neck.

March 31: Wassermann, negative. A trace of protein in the urine.

April 12: Moderate conjunctivitis, skin red, with diffuse dark papules, slight desquamation. Liver, palpable. Blood pressure, 96/60. Urine contains a trace of bile pigment and protein.

April 25: Marked generalized desquamation. Liver, 2 inches below costal margin. Spleen, enlarged. Several abscesses on thighs and neck. No trace of arsenic in 50 gm. of skin flakes.

May 16: Abscesses healed. Desquamation slight. Skin markedly pigmented. Blood pressure, 125/80. Liver and spleen as before. Temperature, from 99 to 103 F. for past three weeks. Complains of numbness in feet. White blood cells, 14,000.

June 9: Urine free from bile pigment, bile salts, protein, leucin, tyrosin and casts. Wassermann, negative. No arsenic found in urine 135 days after last injection.

July 17: Chemical blood analysis. General condition greatly improved.

CASE 23.—Male, aged 23. Feb. 27, 1919: Chancre.

May 5, 1919: Had received novarsenobillon, 2.85 gm., and mercury, 0.32 gm., in five treatments with intervals of seven days. This was immediately followed by a severe generalized dermatitis, associated with marked desquamation and numerous small abscesses. Urine contained a trace of protein.

April 25: Deep pigmantation of skin; fine branny desquamation. Liver and spleen enlarged. Blood pressure, 115/70. Loss of finger nails. Urinalysis normal. No arsenic found in urine seventy-four days after last injection. July 17: Chemical blood analysis. General condition improving; still a bed patient.

CASE 24.—Male, aged 22. June 13, 1919: Deeply jaundiced. Urine contains bile pigment, protein and granular casts. No history of syphilis or of treatment.

July 2, 1919: Deeply jaundiced, liver and spleen palpable; indefinite pains in liver region; stools clay colored; appetitie, good; Wassermann, negative.

August 17: Chemical blood analysis. Condition unchanged, excepting for the absence of protein and casts in the urine.

CASE 25.—Male, aged 21; weight, 160 pounds. Feb. 12, 1919: Had received novarsenobillion, 5.45 gm., and mercury, 0.648 gm., in ten treatments with intervals of seven days.

August 1: Anorexia, nausea and jaundice. Liver and spleen not enlarged. Urine contains bile pigment and bile salts. No arsenic found in urine 125 days after last injection.

August 17: Chemical blood analysis. General condition fair; slightly jaundiced; liver not enlarged.

CASE 26.—Male, aged 21. April 21, 1919: Chancre.

June 12, 1919: Had received novarsenobillon, 6.4 gm., and mercury, 0.71 gm., in eleven treatments with intervals of seven days.

June 29: Chills, weakness, abdominal cramps, constipation and jaundice. Wassermann, negative.

July 7: Complains of weakness; jaundice persists; liver, palpable. No arsenic found in urine thirty-five days after last injection.

July 17: Chemical blood analysis. Condition unchanged.

CASE 27.—Male, aged 25. Feb. 9, 1919: Chancre.

March 17, 1919: Had received novarsenobillon, 4.05 gm., and mercury, 0.45 gm., in seven treatments with intervals of seven days.

June 13: Weakness, constipation and jaundice.

July 8: Deeply jaundiced. Liver, slightly enlarged. No arsenic found in urine ninety days after last injection.

July 17: Chemical blood analysis. General condition slightly improved.

CASE 28.—Male, aged 34. No history of infection. April 10, 1919: Developed a generalized maculopapular eruption. Wassermann, strongly positive.

June 23, 1919: Had received novarsenobillon, 4.05 gm., and mercury, 0.45 gm., in seven treatments with intervals of seven days.

June 27: Nausea, vomiting and jaundice.

July 8: Jaundiced; liver, palpable; urine contains bile pigment; no complaints. No arsenic found in urine twenty-four days after last injection.

July 17: Chemical blood analysis. General condition unchanged.

CASES 29 to 34.—These patients were recovering from illnesses other than toxic jaundice, and at the time of the chemical blood analyses were still in a weakened condition.

CASES 35 to 40.—These men were apparently in good health at the time of the chemical blood analyses.

METHODS EMPLOYED

A complete twenty-four hour specimen of urine was collected from each patient on the day preceding the blood analysis. On these specimens were determined the volume, reaction, specific gravity, protein, sugar, bilirubin, bile salts, urobilinogen, urobilin, uric acid and the microscopic contents.

Synchronous blood and urine specimens were collected on the following morning before breakfast, by the following method: At 6 a. m. the patient completely emptied his bladder; at 7:30 a. m., from 30 to 40 c.c. of blood was aspirated, by venipuncture, into a bottle containing potassium oxalate crystals (20 drops of 20 per cent. potassium oxalate solution evaporated on the bottom and sides of the bottle); at 9 a. m., the three-hour specimen of urine was collected. In some cases, when the urinary excretion was low, a glass of water was given during this period.

The following estimations were made on the whole blood: Sugar, creatinin, cholesterol, urea nitrogen, uric acid and bile salts. Bilirubin tests were made on the plasma.

On the three hour specimens of urine, the following determinations were made: Rate of excretion, reaction, specific gravity; the presence of bile salts and protein, and, quantitatively, sugar, uric acid, urobilinogen, urobilin and bilirubin.

Sugar in the urine was estimated quantitatively by Myers' method,[10] bilirubin, by Hooper and Whipple's modification of Huppert's reaction;[11] bile salts were estimated by Hay's sulphur test. Urobilinogen was tested by extracting with amyl alcohol after developing the color in the urine by the use of Ehrlich's reagent; diluting to a suitable volume with amyl alcohol, and obtaining relative quantitative figures by matching against a standard solution in a Hellige colorimeter. The relative rate of excretion was obtained by multiplying this figure by the c.c. per hour of urine and dividing by 1,000.

Urobilin estimations in the urine were made by extracting with amyl alcohol and adding to this an ammoniacal alcoholic solution of zinc chlorid; relative quantitative figures were obtained by repeated alcoholic dilutions until no fluorescence could be detected on examining in sunlight against a black background. The relative rate of excretion was obtained by multiplying the dilution by the c.c. per hour of urine and dividing by 100. The relative oxidation of urobilinogen was obtained by dividing urobilin by urobilinogen. Uric acid in the urine was quantitatively determined by the method of Benedict and Hitchcock.[12] Blood sugar estimations were made by a modification of the Lewis and Benedict method.[13]

Creatinin in the blood was estimated by Folin's method as modified and described by Myers and Killian.[14] Blood cholesterol was deter-

10. Myers, V. C.: Proc. Soc. Exper. Biol. & Med. **13**:178, 1916.
11. Hooper, C. W., and Whipple, G. H.: Am. J. Physiol. **40**:332, 1916.
12. Benedict, S. R., and Hitchcock, E. H.: J. Biol. Chem. **20**:619, 1915.
13. Myers, V. C., and Bailey, C. V.: J. Biol. Chem. **24**:147, 1915.
14. Myers, V. C., and Killian, J. A.: Am. J. M. Sc. **157**:674, 1919.

mined by the method described by Myers and Wardell,[15] urea nitrogen in the blood, by Van Slyke and Cullen's modification of Marshall's method;[16] uric acid in the blood, by the Folin and Denis-Benedict method as described by Myers and Fine.[17]

The presence of bile salts in the blood was determined by applying Pettenkofer's test to the supernatent fluid, after the precipitation of the purins, in the method for estimating the blood uric acid; 10 c.c. of blood was used in this test. Gmelin's test for bilirubin was applied directly to the plasma. Bilirubin in the plasma was also estimated by the method described by Blankenhorn [5] and found to correspond with the results of Gmelin's test. The method consists in diluting the plasma until a color can barely be detected in a column 1 cm. deep; the number of dilutions is the bilirubin index.

A modified Gutzeit's test [18] was used for arsenic, 50 c.c. of urine being employed.

DISCUSSION

Excretion of Arsenic.—No arsenic was found in the urine of any of these patients; tests were made at periods varying from 24 to 157 days after the last treatment.

Analyses of Twenty-Four-Hour Urines. — The twenty-four-hour urines of all these patients were free from protein and pathologic sediment. No bile salt was indicated by Hay's test. Six of the patients clinically jaundiced had bile pigment in the urine; the method used was found unsuitable for accurate quantitative determination of small quantities.

The relative rate of excretion of urobilinogen and the relative oxidation of this substance to urobilin are shown in Table 1, and will be referred to later. The daily excretion of sugar is shown in Table 1 to be normal in all of the cases [19]— the amount not being detectable by ordinary methods. The daily excretion of uric acid was much greater in the more severe cases.

Bilirubin, Urobilinogen, Urobilin.—In eleven cases, bile pigment was found in the plasma and, as a rule, in these cases bile salts were also found, although a few cases showed dissociation. The extent of the jaundice did not correspond with the severity of the illness.

In Table 3 the cases are grouped according to the presence or absence of bilirubin in the plasma; cases not associated with disordered liver are classified by the presence or absence of debility. The greatest

15. Myers, V. C., and Wardell, E. L.: J. Biol. Chem. **36**:147, 1918.
16. Van Slyke, D. D., and Cullen, G. E.: J. Biol. Chem. **19**:211, 1914.
17. Myers, V. C., and Fine, M. S.: J. Biol. Chem. **20**:391, 1915.
18. Simon, W.: Manual of Chemistry, New York, 1916.
19. Bailey, C. V.: Arch. Int. Med. **23**:455 (Oct.) 1919.

excretion of urobilinogen and urobilin was noted in the jaundiced cases; in the liver cases which were free from jaundice the output of this pigment was less than half. Among the cases not associated with liver disturbance, the debilitated patients had twice the excretion of the well patients. A relatively higher rate of excretion of urobilinogen and urobilin was present in the early morning than, on the average, during the day. This was most marked in the severe cases, the early morning rate being 19.66 per hour, while for the twenty-four-hour period the rate was 13.4 per hour. The difference in the liver cases in which improvement was noted was less marked, being 8.6 per hour in the morning and 7.6 per hour in the twenty-four-hour specimens.

TABLE 1.—Twenty-Four-Hour Urine

Case	Volume, C.c.	Bilirubin	Total Relative Excretion		Relative Oxidation of Urobilinogen	Uric Acid		Sugar, Gm. in 24 Hrs.
			Urobilinogen	Urobilin		Gm. in 24 Hrs.	Mg. per Hr.	
1	2,300	—	565.8	20.7	0.04	0.65	27.0	1.61
2	2,210	—	165.75	24.31	0.15	0.975	40.62	1.69
3	1,260	—	191.52	10.08	0.05	0.945	39.37	1.33
4	1,325	—	250.42	19.87	0.08	0.903	37.62	1.67
5	1,495	—	55.31	17.94	0.32	0.57	23.75	1.02
6	1,005	—	55.27	11.05	0.2	0.65	27.0	1.18
7	1,424	—	148.00	240.2	1.68	0.726	30.25	1.28
8	1,480	—	325.6	22.2	0.07	0.518	21.58	1.48
9	1,120	—	259.8	20.72	0.08	0.683	28.45	1.32
10	1,520	—	161.12	9.12	0.06	0.744	31.0	2.55
11	1,150	—	188.6	63.25	0.34	0.57	23.75	1.28
12	1,000	—	54.4	16.0	0.29	0.48	20.0	0.67
13	2,350	—	65.8	18.8	0.28	0.607	25.29	1.03
14	1,450	—	79.75	26.1	0.33	0.75	31.25	0.84
15	2,150	—	75.25	217.15	2.85	0.47	19.58	0.73
16	660	—	192.06	27.06	0.14	0.56	23.33	0.9
17	1,300	—	54.6	16.9	0.31	1.35	56.25	1.17
18	1,150	—	138.0	33.35	0.24	.....	.....	1.56
19	2,315	+++	451.42	131.95	0.29	.....	.....	1.39
20	1,470	—	51.45	42.63	0.83	0.715	29.79	0.88
21	740	+	63.64	66.16	1.04	.....	.....	1.18
22	1,470	—	52.92	164.64	3.11	1.4	58.33	1.23
23	2,030	—	36.54	64.96	1.77	0.574	23.91	1.14
24	1,700	++	58.4	149.6	1.69	0.83	34.58	1.22
25	1,150	++++	414.0	146.0	0.35	1.1	45.83	2.76
26	1,050	—	25.2	115.5	4.58	0.743	30.95	1.28
27	1,800	++	594.0 —	273.6	0.47	1.75	72.91	2.41
28	1,470	++++	117.6	211.68	1.8	1.62	67.5	2.47

Oxidative Activity of the Urine.—In the voided urine, the relative oxidation of urobilinogen to urobilin was greatest in the well patients and least in the severe liver cases, indicating either the presence of a protecting substance or of a decreased excretion of oxidase in these cases. The latter is the probable explanation as in similar conditions—poisoning by phosphorus, chloroform, etc.—there is a decrease of oxidation in the body, as shown by the respiratory exchange and the presence of incompletely oxidized bodies in the urine.[20] In Table 3 the figures indicate not only a decreased excretion of oxidase in the liver cases, but also in debilitating conditions not clinically associated

20. Wells, H. G.: Chemical Pathology, Philadelphia and London, 1918, p. 542.

with disordered liver. Absolute rest seems to increase the excretion, and probably the production of oxidase; in the twenty-eight liver cases the oxidative activity in the urine was greater in the early morning than in the twenty-four-hour specimens in the proportion of 59 to 49.

Cholesterol.—Of greater interest is the concentration of cholesterol in the blood. In the twelve cases not associated with disordered liver, the percentage varied from 0.117 to 0.21, giving an average of 0.155 per cent., which compares favorably with Gorham and Myer's fourteen normal cases with an average of 0.15 per cent., using the same method.[21] Of the patients with catarrhal jaundice, one (Case 20) had recovered and showed a blood cholesterol of 0.153 per cent.; a second patient (Case 24) was still deeply jaundiced and had a slight increase of this substance in his blood (0.184 per cent.). The blood cholesterol in the case of syphilitic hepatitis is slightly above the average normal. In the twenty-five cases of toxic jaundice, the cholesterol value is strikingly high, giving an average of 0.235 per cent., the values varying from 0.165 per cent. in a patient apparently recovered, to 0.292 per cent. in a recent case. In 84 per cent. of these cases, the value is over 0.2 per cent. In Table 3 one sees that the greatest concentration of cholesterol in the blood occurred in the cases in which bile pigment was found in the plasma. Hypercholesterolemia, however, was found in nearly all of the toxic cases and was present in the patients free from symptoms, while still under hospital treatment. It seems to be an early and marked sign of toxic jaundice and its presence may be a valuable sign of a precarious state of the liver in these cases.

Sugar.—No disturbance of carbohydrate metabolism was discovered. The values for blood sugar are normal; in the last six cases the values are above normal, but these patients were examined three hours after breakfast and were influenced by alimentation. The excretion of sugar at the time of the blood analyses and for the twenty-four-hour period was at the normal rate.[19]

Blood Urea and Creatinin.—A study of the nonprotein nitrogenous constituents of the blood is complicated by the high protein diets and the varying physical restrictions placed on these men. The values for urea nitrogen in the last six cases, the patients apparently being in good health, are within the upper normal limit, which is 20 mg. per hundred c.c. of blood.[22] Of the remaining cases, some show normal values, but the majority are above normal, one as high as 49 mg. per hundred c.c. That this increase is in part due to impaired elimination by the kidneys is shown by the fact that, with few exceptions, the cases with a urea nitrogen exceeding 20 mg. per hundred show a slight

21. Gorham, F. D., and Myers, V. C.: Arch. Int. Med. **20**:599 (Nov.) 1917.
22. Kast, L., and Wardell, E. L.: Arch. Int. Med. **22**:581 (Nov.) 1918.

TABLE 2

Case	Day of Illness	Blood								Urine			
		Bilirubin		Bile Salts	Cholesterol, per Cent.	Sugar, per Cent.	Gm. per 100 C.c.			Sugar, Gm. per Hr.	Uric Acid, Mg. per Hr.	Index of Uric Acid Excretion*	Bilirubin
		Gmelin's Test	By Dilution of Plasma				Creatinin	Urea N	Uric Acid				
1	239	—	...	—	0.171	0.080	2.2	40	4.41	0.06	23.86	0.18	—
2	92	—	...	—	0.165	0.102	2.85	22	4.9	0.046	20.87	0.23	—
3	81	—	...	—	0.263	0.1	2.6	32	3.3	0.06	25.88	0.127	—
4	89	—	...	—	0.279	0.09	2.4	33	4.7	0.036	28.56	0.17	—
5	13	—	...	—	0.233	0.118	3.2	37	4.2	0.036	9.08	0.466	—
6	55	—	16	+	0.208	0.096	1.98	22	3.67	0.056	32.2	0.114	—
7	54	—	8	—	0.203	0.102	1.94	24	2.11	0.044	43.1	0.049	—
8	136	—	12	—	0.233	0.1	1.96	27	2.46	0.015	8.21	0.3	—
9	84	+	30	—	0.267	0.11	2.22	24	3.7	0.035	19.2	0.2	—
10	69	—	12	—	0.193	0.1	2.1	23	3.57	0.044	28.11	0.127	—
11	83	+	24	—	0.292	0.118	2.5	31	2.5	0.054	19.3	0.13	—
12	122	—	14	—	0.275	0.106	2.4	43	3.87	0.234	10.13	0.387	—
13	66	—	10	—	0.205	0.112	2.6	30	3.57	0.080	63.5	0.056	—
14	70	—	10	—	0.203	0.092	2.26	28	5.0	0.046	27.8	0.178	—
15	90	—	14	—	0.212	0.1	2.58	31	4.78	0.147	66.0	0.072	—
16	58	—	14	—	0.208	0.108	2.02	33	1.76	0.050	22.6	0.076	—
17	113	—	8	—	0.258	0.094	2.41	15	4.34	0.060	96.7	0.045	—
18	85	—	12	—	0.175	0.096	1.76	12	5.55	0.033	.....	.....	—
19	45	+++	150	+	0.222	0.108	1.74	8	1.94	0.048	56.7	0.034	+++
20	19	++	60	—	0.153	0.108	1.54	11	3.12	0.032	20.5	0.156	—
21	45	+	40	+	0.292	0.096	1.8	14	5.31	0.034	60.5	0.057	+
22	170	—	12	—	0.285	0.124	2.13	14	5.0	0.045	44.6	0.11	—
23	74	+	50	+	0.17	0.12	2.8	30	3.0	0.07	44.6	0.066	—
24	34	+++	120	+	0.184	0.084	1.5	20	3.7	0.054	50.0	0.074	++
25	16	+++	80	+	0.24	.....	1.8	36	6.3	0.2	168.6	0.037	++++
26	18	+	50	+	0.292	.....	1.7	16	2.39	0.148	95.0	0.025	—
27	34	++	80	++	0.275	.....	1.3	29	3.1	0.052	66.0	0.047	++
28	20	++	90	+++	0.237	0.116	1.2	39	1.5	0.055	53.4	0.028	++++
29	...	—	...	—	0.21	0.1	2.3	36	5.54	0.03	31.0	0.178	—
30	...	—	...	—	0.12	0.102	2.0	34	6.4	0.027	26.2	0.246	—
31	...	—	...	—	0.16	0.112	2.1	36	2.3	0.105	103.1	0.022	—
32	...	—	...	—	0.18	0.106	1.9	47	3.3	0.052	27.3	0.037	—
33	...	—	...	—	0.15	0.1	1.98	41	5.45	0.104	89.4	0.2	—
34	...	—	...	—	0.117	0.088	1.84	49	3.23	0.096	64.0	0.05	—
35	...	—	...	+	0.19	0.124	2.3	16	2.32	0.014	8.0	0.29	—
36	...	—	...	—	0.12	0.112	2.1	18	3.0	0.03	34.0	0.085	—
37	...	—	...	—	0.17	0.12	2.0	19	3.3	0.035	47.2	0.07	—
38	...	—	...	—	0.137	0.12	2.1	20	2.4	0.028	35.6	0.066	—
39	...	—	...	—	0.15	0.118	2.1	18	5.6	0.033	54.8	0.1	—
40	...	—	...	—	0.16	0.128	2.1	20	1.7	0.024	35.7	0.046	—

* Milligrams per 100 C.c. of blood divided by milligrams per hour excreted.

TABLE 2

—Urine			Diet						
Relative Excretion Rate per Hr.		Relative Oxidation of Urobilinogen	Protein			Fat, Gm.	Carbohydrate, Gm.	Diagnosis	Remarks
Urobilinogen	Urobilin		Animal, Gm.	Vegetable, Gm.	Total, Gm.				
52.64	2.24	0.04	90	60	150	152	435	Syphilitic hepatitis	
3.18	0.73	0.23	90	60	150	152	435	Toxic jaundice	Debilitated; unrestricted; up and about
1.37	0.66	0.48	90	60	150	152	435	Toxic jaundice	
3.68	0.80	0.22	90	60	150	152	435	Toxic jaundice	
1.85	1.46	0.79	90	60	150	152	435	Toxic jaundice	
4.94	1.25	0.25	82	59	141	106	450	Toxic jaundice and furunculosis	
4.48	3.28	0.73	90	60	150	152	435	Toxic jaundice	Confined to hospital ward
9.47	0.27	0.03	95	9	104	124	282	Toxic jaundice	
9.72	0.36	0.04	95	34	129	136	380	Toxic jaundice	
2.22	0.44	0.20	90	60	150	152	435	Toxic jaundice	
4.62	10.22	2.21	90	60	150	152	435	Toxic jaundice	
1.07	2.04	2.84	90	60	150	152	435	Toxic jaundice and furunculosis	
4.08	2.52	0.63	90	60	150	152	435	Toxic jaundice	Debilitated; unrestricted; up and about
4.66	8.08	1.73	90	60	150	152	435	Toxic jaundice	
11.54	7.35	0.64	90	60	150	152	435	Toxic jaundice and nephritis	
4.53	5.78	1.27	90	60	150	152	435	Toxic jaundice	
16.25	5.31	0.33	123	35	158	147	366	Toxic jaundice and dermatitis	
8.9	4.24	0.48	123	35	158	147	366	Toxic jaundice and dermatitis	
33.38	3.45	0.10	72	53	125	105	392	Toxic jaundice	
2.34	4.75	2.03	98	37	135	122	414	Catarrhal jaundice	
7.68	6.92	0.90	117	32	150	35	386	Toxic jaundice and dermatitis	
3.25	6.35	1.95	124	33	157	147	353	Toxic jaundice and dermatitis	Confined to hospital ward
3.4	5.8	1.70	102	59	161	118	480	Toxic jaundice and dermatitis	
2.7	7.02	2.82	136	52	188	130	438	Catarrhal jaundice	
22.81	16.28	0.71	90	60	150	152	435	Toxic jaundice	
17.55	11.7	0.66	90	60	150	152	435	Toxic jaundice	
12.94	7.0	0.54	109	80	189	162	643	Toxic jaundice	
20.44	4.6	0.22	115	80	195	164	643	Toxic jaundice	
1.45	1.86	1.28	90	60	150	152	435	Bronchitis	
1.33	5.06	3.80	90	60	150	152	435	Disordered action of the heart	
8.14	4.62	0.56	90	60	150	152	435	Meningitis	Debilitated; unrestricted; up and about
2.47	5.98	1.15	90	60	150	152	435	General debility	
5.2	11.90	4.84	90	60	150	152	435	Syphilis and tonsillitis	
10.92	4.62	0.42	90	60	150	152	435	Constipation	
0.53	1.18	2.23	90	60	150	152	435	Influenza	
1.06	1.12	1.06	90	60	150	152	435	Arthritis	
1.41	2.4	1.70	90	60	150	152	435	Gastritis	Recovered; unrestricted; up and about
1.17	2.68	2.29	90	60	150	152	435	Normal	
1.7	3.12	1.83	90	60	150	152	435	Sciatica	
1.19	1.93	1.62	98	53	151	133	429	Normal	

increase in blood creatinin and uric acid and a decreased excretion of uric acid as shown by the ratio of excretion to blood concentration. These patients were all more or less debilitated and their high protein diet probably accounts for most of the urea nitrogen increase. Unfortunately, the excretion of urea was not estimated.

Uric Acid.—The relationship between the concentration of uric acid in the blood and the rate of excretion (mg. per hundred c.c. of blood divided by mg. per hour excreted) is of interest in considering the blood uric acid. It has frequently been demonstrated that uric acid is the most difficult of the nitrogenous waste products to eliminate, and that one of the first signs of failing kidney function is an increase of this substance in the blood.[23] Accepting 3 mg. per hundred c.c. of blood as being the normal upper limit, we find that in 67 per cent. of the first twenty-eight cases abnormally high blood uric acid was noted. In only 14 per cent. of these cases did we find a uric acid excretion index above 0.2 (Watanabe's figure of slightly impaired kidney function[24]), and in many cases (Nos. 15, 17, 21 and 25) we found a very free excretion associated with a high concentration in the blood, pointing to an increased production of uric acid. As the diet was low in purins and none of these patients had a leukocytosis at the time of examination, one naturally thinks of liver nuclear substance as the source of this uric acid.

TABLE 3

Case	Urobilinogen	Urobilin	Combined Excretion	Relative Oxidation of Urobilinogen	Blood Cholesterol, per Cent.
Liver cases having bile pigment in plasma—9, 11, 19 to 21, 23 to 28.....	12.5	7.16	19.66	57	0.238
Improved liver cases, no bile pigment in plasma—2 to 8, 10, 12 to 18, 22....	5.34	3.26	8.6	61	0.224
Debilitated cases, not associated with disordered liver—29 to 34.....	4.92	5.68	10.6	115	0.156
Recovered cases, not associated with disordered liver—35 to 40.....	1.18	2.07	3.25	175	0.154

Effect of Exercise.—The deleterious effect of exercise on debilitated patients is well shown in Table 4. In the first group, constituting the more serious cases, the urea nitrogen is practically normal; so also the creatinin. There is a slight increase in blood uric acid, but the excretion is very good. These patients were confined to their wards. The second group is made up of patients who had apparently recovered. The diet of this group is 4 per cent. richer in protein, but the

23. Myers, V. C., Fine, M. S., and Lough, W. G.: Arch. Int. Med.: **17**:570 (May) 1916. Baumann, L., Hansmann, C. H., Davis, A. C., and Stevens, F. A.: Arch. Int. Med **24**:70 (July) 1919.

24. Watanabe, C. K.: Am. J. M. Sc. **154**:76, 1917.

blood analyses show 57 per cent. more urea nitrogen, 9.2 per cent. more uric acid, 37 per cent. more creatinin, and a little more than one-half the ability to excrete uric acid as shown by the index; these patients, being apparently well, were unrestrained. Reference will be made later to the association of glycogen in the liver with a protection of that organ against poisonous substances. It may be stated, however, that the susceptibility of the liver to the destructive action of circulating toxins is in inverse proportion to the amount of glycogen contained in that organ. Hammarsten and Hedin [25] point out the fact that, during rest, the glycogen content of the liver is greatly increased, and that it is diminished during work. In dogs, Külz found the liver glycogen reduced to a minimum after a period of a few hours hard work. Considering this with the results shown in Table 4, we see that in the debilitated patients the effect of exercise is to decrease the excretory power of the kidneys, increase the waste products in the blood, and lower the resistance of the liver to toxins.

TABLE 4

Cases	Blood			Index of Uric Acid Excretion*	Protein in Diet		
	Uric Acid, Mg. per 100 C.c. of Blood	Urea N, Mg. per 100 C.c. of Blood	Creatinin, Mg. per 100 C.c. of Blood		Animal, Gm. per Day	Vegetable, Gm. per Day	Total, Gm. per Day
Liver cases, confined to hospital ward—6 to 10, 17 to 28	3.57	21.0	1.87	0.064	98	46	144
Liver cases; debilitated; unrestricted; up and about—1 to 5, 11 to 16	3.9	33.0	2.57	0.121	90	60	150
Debilitated cases, not associated with disordered liver; up and about—29 to 34	4.37	40.5	2.02	0.077	90	60	150
Recovered cases, not associated with disordered liver; up and about—35 to 40	3.05	18.5	2.1	0.086	91	59	150

* Milligrams per 100 C.c. of blood divided by milligrams per hour excreted.

In this type of poisoning, decreased oxidative activity has been held accountable for the free autolysis occurring in the liver.[26] Our figures indicate an increased oxidative activity during absolute rest and are a further plea for rest during the treatment of these patients.

A possible explanation of the "delay" in poisoning by arsenobenzol, chloroform, etc., presents itself. Harrison [1] suggests that each dose of arsphenamin contributes its quota of damage to the liver, and that a final dose precipitates the toxic symptoms. In many cases, however, the toxic symptoms do not appear for weeks after the last treatment. It seems quite possible that in these cases the damaged organs are

25. Hammarsten and Hedin: Physiologiacl Chemistry, London and New York, 1915, p. 391.

26. Wells, H. G.: J. A. M. A. **46**:341 (Feb. 3) 1906.

able to functionate during the course of treatment, when dietetic and physical restrictions are imposed; but when these are removed, and the patient returns to work and an unrestricted diet, the straw "which breaks the camel's back" has been added and toxic symptoms appear. This is well illustrated in Case 19. The patient had received 4.05 gm. of novarsenobillon in seven weekly doses; during the treatment, and for the following three weeks, he remained in the hospital and had no toxic symptoms. He was given seven days leave, however, and returned toxic and jaundiced. Similar observations were made in the case of another patient (Case 8). Assurances were given by each of these men that their lives were abstemious during their absence.

Clinical Application.—From the above results it would seem that, in addition to considering the protein intake of these patients, we must carefully regulate their exercise. Physical examination fails us in classifying these cases, and resort must be had to some functional test if we are to avoid toxic symptoms. In Table 4 the index of uric acid excretion appears to be the best test, but the labor entailed tends to preclude it as a routine method. The estimation of the urea in the blood is the second choice, and its routine use in institutional treatment is quite practicable. An abnormally high value in a patient at rest would be an indication for reducing the protein in the diet, while similar results in "up patients" would, perhaps, call for both rest and protein restriction.

Diet in the Treatment of Syphilis.—Experimental toxic jaundice has added greatly to our knowledge of liver damage and repair. The lesions produced in the liver by arsenobenzol derivatives are similar to those produced by chloroform and phosphorus, being essentially a fatty infiltration, with more or less necrosis of the liver cells. Opie and Alford [27] have shown that in both chloroform and phosphorus poisoning, less damage is done to the liver if a carbohydrate diet is given. Graham [28] demonstrated that in dogs the resistance of the liver to chloroform is proportional to the amount of glycogen in that organ. Rettig [29] has made similar observations in connection with phosphorus poisoning.

Many interesting and practical observations, which might well be applied to the toxic cases under discussion, have been made by Davis and Whipple [30] from their experiments on liver destruction and repair in dogs poisoned by chloroform. Their findings may be summarized as follows: (1) In starvation, a maximal injury to the liver is to be

27. Opie, E. L., and Alford, L. B.: J. A. M. A. **62**:295 (Jan. 24) 1914.
28. Graham, E. A.: J. Exper. Med. **21**:185, 1915.
29. Rettig, H.: Arch. f. exp. Path. u. Pharmakol. **76**:345, 1914.
30. Davis, N. C., and Whipple, G. H.: Arch. Int. Med. **23**:612 (May) 1919.

expected. (2) Sugar and diets rich in carbohydrates, fed in the days preceding chloroform anesthesia, exert a marked protective action against liver injury. (3) Fats alone, or combinations of food containing fat in large proportion, induce a maximal susceptibility to liver injury. (4) Skim milk alone is highly protective. (5) A diet of bread and skim milk or any rich carbohydrate diet gives the optimum liver repair. (6) A diet of cooked skeletal muscle is not favorable for rapid liver repair. (7) Fat diets do not aid in liver repair.

Lusk [31] has shown that, in phosphorus poisoning, when the body carbohydrates are lowered, protein metabolism is greatly increased. This is explained by Lüthje [32] and Cathcart [33] who conclude that carbohydrates are necessary in the synthesis of protein from the absorbed products of protein digestion. A rich carbohydrate diet would, therefore, ensure a complete assimilation of the protein and call for but a minimum protein intake. In determining this minimum, many factors come into play; these have been considered carefully and applied by Chace and Rose [34] in their dietetic treatment of nephritis. These authors find that 60 gm. of mixed animal and vegetable protein is quite sufficient for patients under treatment, provided the necessary carbohydrate is given to make up their fuel requirements.

It would seem advisable in the treatment of syphilis to institute a rich carbohydrate diet very low in fat and protein. This diet should precede the treatment by several days and should be continued throughout its full course. The high blood urea and the prolonged convalescence in our reported cases emphasize the advisability of such a diet being used.

SUMMARY

A report is made on the chemical blood and urine analyses in twenty-five cases of toxic jaundice following combined arsenical and mercurial treatment for syphilis, on two cases of catarrhal jaundice, on one case of syphilitic hepatitis, and on twelve cases in which patients were recovering from illnesses not associated with the liver.

Arsenic tests were made on the morning urines at periods ranging from 24 to 157 days after the last treatment and none was found. The twenty-four-hour urines were normal, excepting for pathologic pigments in some of the cases.

Patients clinically jaundiced had bile pigment in their urine. Bilirubin estimations in the plasma, according to Blankenhorn's dilution method, compared favorably with Gmelin's tests and the clinical findings.

31. Lusk, Graham: Am. J. Physiol. **1**:5, 1898.
32. Lüthje, H.: Arch. ges. Physiol. **113**:547, 1906.
33. Cathcart, E. P.: J. Physiol. **39**:311, 1909.
34. Chace, A. F., and Rose, A. R.: J. A. M. A. **69**:440 (Aug. 11) 1917.

Of the liver cases, those patients with bilirubin in the plasma excreted more than twice as much urobilinogen as did those patients who were free from jaundice; the nonjaundiced liver patients excreted more than twice as much as the well persons. Of the cases not associated with disordered livers, the debilitated patients had more than twice the urobilinogen excretion of the well persons.

In the twenty-eight liver cases, the rate of excretion of urobilinogen was one third greater in the early morning than was the average rate during the day.

In the urines, the relative oxidation of urobilinogen to urobilin was greatest in the well persons, less in the debilitated persons; about one third as much in the nonjaundiced liver patients, and still less in the jaundiced liver patients. The relative oxidation was greater in the early morning than in the twenty-four-hours specimens.

The patients with toxic jaundice had a marked increase in blood cholesterol, the jaundiced patients (being also the severe cases) had the greatest increase. In the cases not associated with liver disturbance the cholesterol value was normal.

Sugar estimations in blood and urine revealed no disorder of carbohydrate metabolism.

Blood creatinin estimations showed no marked departure from the normal. Uric acid estimations in the blood and urine indicated an increased production of this substance.

The values for urea nitrogen are normal in the well persons. Of the remaining cases, some patients show normal values, but the majority are above normal. This seems to be due to the high protein diet and deficient physical restrictions placed on these men.

The effect of exercise on debilitated patients seems to decrease the excretory power of the kidneys, increase the waste products in the blood, and lower the resistance of the liver to toxins. This, associated with an increase in the diet proteins, is given as an explanation of the "delay" in poisoning by arsenobenzol, chloroform, etc. Arguments are advanced for the adoption of a diet rich in carbohydrate and very low in fat and protein in the treatment of syphilis.

CONCLUSIONS

1. In patients whose livers are damaged by arsenobenzol derivatives, an increase of cholesterol in the blood is an early and marked sign; it persists after other clinical signs have disappeared; its routine estimation may be of value in detecting the onset of liver injury in patients under antisyphilitic treatment.

2. In debilitated patients, the oxidative activity of the urine is decreased. This decrease is much more marked if the liver is disordered. In such cases the oxidative activity is greatest during absolute rest.

3. Exercise should be restricted greatly during the course of antisyphilitic treatment and for the following few weeks.

4. A diet, rich in carbohydrate and very low in fat and protein, should precede, accompany and succeed the administration of arsenobenzol derivatives in the treatment of syphilis.

5. Increase of protein in the diet, and of exercise, should be controlled by the estimation of the urea in the blood.

6. The appearance of toxic symptoms in delayed poisoning by arsenic, phosphorus, chloroform, etc., is possibly due to the premature increase of protein in the diet, and of exercise in these cases.

We wish to thank Lieut.-Col. C. F. Martin, Lieut.-Col. G. S. Strathy, Major Wallace Wilson, Major W. H. Tytler and Capt. Beverley Hannah of the C. A. M. C., for expediting this work, and Prof. E. P. Cathcart and Dr. G. H. Paul for suggestions in the preparation of the manuscript.

303 East Twentieth Street, New York. 227 Delatre Street, Woodstock, Ontario, Canada.

A CASE OF HEREDITARY DIABETES.*

FREDERICK M. ALLEN, M.D., AND J. W. MITCHELL, M.D.
LAKEWOOD, N. J.

As the cause of hereditary or familial diabetes is of interest for the subjects of both diabetes and heredity, the opportunity was taken of making some observations concerning it is one case on the diabetic service of this hospital.

REPORT OF CASE

Family History.—The family are "poor whites" in a little mountain hamlet of South Carolina, and offer three features of special interest for a study of heredity. First, is the isolation of the community, the absence of immigration, and the thorough knowledge concerning their ancestry and relatives for several generations back. Second, is the large size of the family, and the remarkably high incidence of diabetes encountered in one generation. Third, is the fact that before his marriage to the mother of the present family of children, the father had had an illegitimate child by another woman, which developed diabetes, though that woman and her family were free from diabetes. This, and the diabetes in the father's brother, indicated that the diabetic heredity came through the father.

Personal History.—Mumps, measles, chickenpox, whooping cough and smallpox before the age of 10 years. Otherwise healthy; lived the usual life of the family, doing mostly farm labor. Rather thin and undernourished like the others; no dietary excesses; no alcohol; moderate tobacco. No trauma. Venereal disease or exposure denied.

Present Illness.—In 1915 there appeared polydipsia and polyuria without polyphagia or other symptoms. Sugar was found in the urine, and the diagnosis made promptly, but the patient continued at work without dietary restriction, feeling well notwithstanding continuous glycosuria. Cough began in 1915 and continued thereafter but was not regarded as serious. Fistula in ano in November, 1917. In April, 1918, the patient was drafted, sent to a camp, examined and passed. He said nothing about his diabetes and cough for fear of appearing unpatriotic. He performed the regular duties of his company, which happened to be light, and was sent overseas in August. In England he had to fall out on a three mile "hike" because of backache and weakness, but was transported to France and did full duty for three months, till hard marching was begun and he again had to fall out. He was sent to a field hospital for supposed heart trouble, where the diagnosis was made but no dietetic treatment given. There was rapid progressive loss of weight, and he was shipped for America in bedridden condition in October, 1918. The ship doctor instituted carbohydrate-free diet as far as possible, and the patient improved enough during the trip to walk a little. After landing, he was on ordinary mixed rations for two weeks, and was admitted to this hospital, October 30, on a stretcher in critical condition from both weakness and acidosis.

Physical Examination.—Extremely weak and emaciated patient in early stage of coma, but able when roused to answer questions. Temperature, 99 F.; pulse, 120; respiration, 24; blood pressure, 105/75; height, 5 feet 11 inches; weight, normal'y, 70 kg., now 47 kg. Teeth in very bad condition with caries

* From the Diabetic Service, U. S. Army General Hospital, No. 9, Lakewood, N. J.

and pyorrhea; one root abscess. Signs of consolidation in apices of both lungs, extending half-way down on right side. Slight general lymph gland enlargement. Knee jerks absent. Marked myotonia reaction in muscles. Other findings negative.

Laboratory.—Sputum abundant, gray, mucopurulent, thick, but containing no tubercle bacilli or elastic tissue. Urine: albumin negative, acetone and diacetic heavy, sugar 130.6 gm. for twenty-four hours of October 31. Blood plasma: sugar, 0.850 per cent.; nitroprussid, very heavy; carbon dioxid capacity, 23.6 volume per cent.

Treatment and Progress.—The patient entered in the late afternoon, and received only soup and water to capacity. By the next morning his condition was about the same, though the carbon dioxid capacity had fallen to 21.4 volume per cent. Fasting seemed safe from the standpoint of acidosis, but in view of the serious weakness and tuberculosis, a fat-free diet was begun, of 125 gm. carbohydrate and 100 gm. protein, diminishing gradually to 25 gm. carbohydrate and 70 gm. protein November 4. No alkali or alcohol was given. The urinary sugar fell to 4.6 gm. and the plasma sugar to 0.5 per cent., the carbon dioxid capacity rose to 29 volume per cent., and the general condition was much improved. Continuous fasting was then necessary from November 5 to 11 inclusive, to abolish glycosuria. The plasma sugar fell to 0.189 per cent., the carbon dioxid capacity rose to 40 volume per cent., and the nitroprussid reaction almost disappeared from the plasma and urine. It is noteworthy that during this time the patient's strength increased greatly, and the cough and sputum markedly diminished. When it was attempted to give a fat-free diet of 25 gm. protein and 5 gm. carbohydrate, glycosuria promptly returned. In order to bring down the blood sugar and build up tolerance, a three-day fast was imposed, followed by a diet of nothing but 20 gm. protein, increased gradually to 60 gm. November 24. The plasma sugar was then brought to 0.105 per cent. November 30, while all signs of acidosis were absent, and the plasma carbon dioxid remained continuously at a high normal level (60 to 70 volume per cent.) thereafter. Ten gm. carbohydrate was then added, with fat to raise the total calories to 800. With a gradual increase, broken by occasional single fast-days, by December 19 the patient was taking 80 gm. protein and 50 gm. carbohydrate, a total of 1,200 calories. Owing to a tendency to slight hyperglycemia, the carbohydrate was reduced to 30 gm. January 7.

About this time was the stage of maximal improvement lasting about two months. The patient walked to town daily and spent much of each day in the open air. His hunger was fairly well satisfied by a bulky diet, and he took some real pleasure in life. The lowest weight during the rigorous undernutrition was 46 kg. Subsequently, there was a rise as high as 48.6 kg. Invisible water retention is a possible element in such a gain. Continued improvement was impossible in the presence of two factors; one, the tuberculosis, which was at a hopeless stage even for a non-diabetic; the other the patient's ignorance and unreliability, so that he began to break diet frequently as he felt better. In February, on this account, the diet was raised to 1,500 calories, though hyperglycemia, without glycosuria but with traces of nitroprussid reactions, was the necessary result.

During this optimum period the cough and other symptoms of tuberculosis were almost absent, but physical examination indicated a steady advance of the process. Gradually, subacute attacks of cough and pleuritic pain came, lasting a few days each time. Later a moderate pleural effusion appeared on the left side; 10 c.c. of fluid withdrawn with a syringe was clear, sterile, poor in cells, and contained 0.178 per cent. sugar. Sputum examinations remained negative until April 5, after which tubercle bacilli were constantly present.

During the entire time, special attention was paid to the question of possible syphilis. Wassermann tests of the blood and spinal fluid in this hospital, by Capt. Cyrus Field and Lieut. J. W. Sherrill, with various combinations of serum and antigens, were negative. Inactivated serum sent to St.

Analysis of Hereditary Factors in This Case

Persons	Height	Weight	Complexion	Hair	Eyes	Death		Living Age	Wassermann	Glucose Tolerance Test					
						Age	Cause			Dose of Glucose, Gm	Percentages in Blood Plasma				
											Before	½ Hr. After	1 Hr. After	2 Hrs. After	3 Hrs. After
Father's father.....	Similar to father	Similar to father	Light	Flaxen	Blue	Advanced									
Father's mother	Similar to father	Similar to father	Dark	Black	Black	Advanced									
Father.....	5 ft. 9 in.	145-150 170 max.	Dark	Black	Blue	61	Apoplexy								
Two brothers of father	Similar	Similar	Dark	Black	Blue	Middle life	One from hernia, the other from diabetes								
Three sisters of father..	A little shorter	Never obese	Dark	Black	Blue	.....	.....	Well at advanced age							
Mother of illegitimate child	5 ft. 10 in.	Medium or thin	Light	Flaxen	Blue	Unknown									
Illegitimate child (born 8 or 9 years before marriage)	5 ft. 10 in.	Medium of thin	Light	Flaxen	Blue	35	Diabetes several years duration								
Mother's father (also his brothers)	6 ft. 2 in.	Not obese	Light	Flaxen, red beard	Blue	Advanced									
Mother's mother.....	Tall nearly 6 ft.	Not obese	Dark	Dark	Dark	Advanced									
Mother of present children	5 ft. 5½ in.	130	Light	Flaxen	Blue	.....	.....	55	Negative	100	0.113	.....	0.142	0.142	0.106
Fourteen brothers and sisters of mother	Women tall, men over 6 ft.	Not obese	Light	Flaxen	Blue	Advanced age or still living									
Present Children:															
1st, a girl.....	.....	Medium	Light	Flaxen	Blue	12	Fall								
2d, a girl.....	5 ft. 8 in.	Medium	Dark	Black	Blue	26	Diabetes; duration only 5 months								
3d, a girl.....	5 ft. 4 in.	Medium	Dark	Black	Blue	32	Diabetes; duration 3 years								
4th, a boy.....	5 ft. 10 in.	147	Dark	Black	Blue	.....	.....	32, has one healthy child, female, 5 yrs.	Negative	100	0.166 *0.133	0.250 0.217	0.289 0.205	0.166 0.144	0.094 0.089
5th, a girl.....	.....	Medium	Dark	Black	Blue	10	Diabetes; duration only 2 or 3 months								
6th, a boy.....	.....	Medium	.....	.....	....	1 month	Unknown								
7th, a boy.....	6 ft.	180	Light	Flaxen	Blue	.....	.....	25, 6 years in U. S. Army	Negative	100	0.123	0.192	0.156	0.125	0.091
8th, present patient...	5 ft. 11 in.	158	Light	Brown	Blue	.....	.....	23, diabetes known since 1919	Negative in blood and spinal fluid						
9th, a girl.....	5 ft. 7½ in.	130	Light	Flaxen	Blue	.....	.....	19, well	Negative	100	0.123	0.200	0.154	0.109	
10th, a boy.....	Tall	Thin	Medium	Flaxen	Blue	.....	.....	16, well	Negative	75	0.114	.....	0.143	0.102	0.099
11th, a boy.....	Tall	Thin	Dark	Black	Blue	.....	.....	14, well	Negative	50	0.107	.....	0.127	0.116	0.102
12th, a boy.....	Medium	Thin, sickly	Medium	Brown	Blue	9	Diabetes; duration 3 months								
13th, a boy.....	Medium	Medium	Light	Flaxen	Blue	.....	.....	9, well	.....	Refused blood test. Took 75 gm. glucose without glycosuria					

* The lower row of figures represent the sugar percentages in whole blood.

Luke's Hospital, New York, was reported negative by Dr. L. W. Famulener, also a sample sent to the Peter Bent Brigham Hospital, Boston, was found negative by Dr. Charles Walker. Serum and spinal fluid were both reported negative by the Army Medical School, Washington, and by Dr. B. A. Thomas of the Philadelphia Polyclinic, the latter mentioning the use of syphilitic, cholesterinized and acetone insoluble lipoid antigens. The only exceptional findings were a single positive reaction in the serum obtained by Lieut. H. T. Hyman in this hospital, who in an immediate repetition failed to confirm it, and a positive report by Dr. C. C. Warden of Ann Arbor, Mich., who used a special modified method. The globulin test and cell count of the spinal fluid were normal. Careful examinations by the medical and genito-urinary staffs revealed no signs of either acquired or hereditary syphilis, and likewise nothing suspicious was found in specialized dental and nose and throat examinations. Clinical and Wassermann examinations were also uniformly negative in the other individuals of the family as shown in the table.

Acknowledgement is due to the local Red Cross for paying the expenses of several visits by the relatives, which not only were a great comfort to them and the patient but also afforded the opportunity of extending the investigation to all members of the family.

As the tuberculosis became the dominant element in the condition, the diet was slightly relaxed and fast-days omitted, but the average of total calories was always kept below 2,000, not on account of any diabetic danger, but in order to avoid the great lowering of resistance which results from unchecked diabetes. Glycosuria was permitted occasionally during March, and constantly during April. The lowest weight was 44 kg. without edema, indicating that the emaciation had been controlled better than by the usual over-feeding program. May 9 the patient went into what seemed to be normal sleep, and died apparently from weakness within two hours. The blood plasma analyses are shown in Table 2.

TABLE 2.—Blood Plasma Analyses on the Final Days

Date	Sugar, per Cent.	Nitroprussid	CO_2 Capacity, Volume per Cent.
May 4	0.484	Heavy	57.9
May 5	0.555	Heavy	55.1
May 6	0.517	Moderate	62.3
May 7	0.600	Slight	
May 8	0.405	Faint	70.0
May 9	0.041	Negative	76.7

The clearing of sugar and acetone was not explainable by the diet, as the patient ate and apparently digested 60 gm. protein, 20 gm. carbohydrate and 1,800 calories regularly up to the day of death. It did not indicate improvement in the diabetes, but was evidently a terminal phenomenon of exhaustion such as is familiar in dogs. The fact that dogs with severe phloridzin or diabetic acidosis may become free from acetone bodies at the end is one argument against these substances as the cause of death. Malnutrition and tubercular intoxication furnish sufficient reasons for death in the present case, without the necessity of assuming any unknown causes of coma.

NECROPSY

The necropsy was performed immediately, as necessary for the proper study of diabetic pathology. The gross necropsy was performed by Lieut. J. W. Sherrill.

Both pleural membranes were greatly thickened and adherent, except at the bases, where there was about 300 c.c. of clear fluid on each side. The lungs were mostly air-containing, without massive consolidation; but cavi-

ties ranging in size from a pea to a walnut, with well formed walls and full of thick yellow pus, were scattered throughout both, and they were also riddled with small solid tubercles of pinhead to pea size. The abdomen contained about 300 c.c. clear fluid and very little fat. The mesenteric glands were rather prominent but not caseated. The liver weighed 1,200 gm. and was normal and free from visible tubercles. The gall bladder contained about 50 c.c. clear yellow bile and appeared normal. The spleen weighed 125 gm. and contained no visible tubercles or changes in parenchyma. The pancreas was pale, but normal in size, shape and consistency.[1] The kidneys together weighed 300 gm. and appeared normal throughout. Stomach, intestine, adrenals and testicles normal. The skull was not opened.

Microscopic Examinations.—Specimens of the tissues in absolutely fresh condition were taken in formaldehyd and in Zenker solutions, and were sent to Dr. J. Ewing, New York, Dr. F. B. Mallory, Boston, and Dr. A. S. Warthin, Ann Arbor, to whom thanks are due for their courtesy in studying the material. Professor Warthin's report on the organs in general is summarized as follows:

Liver: Brown atrophy; passive congestion; very young miliary tubercles; small celled infiltration of some of the islands of Glisson.

Gallbladder: Chronic catarrhal cholecystitis, slight.

Kidneys: Congestion; cloudy swelling; no glycogen vacuolation of the loops of Henle.

Retroperitoneal Lymph Nodes: Chronic lymphadenitis; numerous miliary tubercles. In the hilum of the lymph glands and through the retroperitoneal fat many xanthelasma cells. Some of the primitive fat lobules completely converted into a lobular organ of these. The ordinary fat tissue shows marked serous atrophy with proliferation of the endothelial and stroma cells.

Spleen: Marked congestion; atrophy of the lymphoid tissue; stroma is increased and there is an endothelial cell proliferation in the sinusoidal spaces. Some of these cells show vacuolation.

Lungs: Congestion; edema; atelectatic and emphysematous areas; one young tubercle.

Bronchial Nodes: Contain many miliary tubercles.

Suprarenals: Hypoplasia of the medulla and lipoidosis of the cortex.

Testes: Simple atrophy; no orchitis.

Heart Muscle: Simple atrophy and fatty infiltration; serous atrophy of the fat; no myocarditis; fatty degeneration.

No evidences of syphilis.

All Levaditi preparations negative.

Specimens of the aorta were unfortunately omitted from the tissues sent to Dr. Warthin, but were included among those sent to the others. All three pathologists were agreed concerning the complete absence of syphilitic changes in all viscera.

The pancreas calls for special notice. A report was received from Warthin, three slides from Mallory and two from Ewing. The general appearance was more or less atrophic. The acini were mostly small, shrunken and nearly empty; but the acinar arrangement was always preserved, a little zymogen was everywhere present, and there was nowhere any actual involution. These appearances belong merely to inanition. They were mentioned by Warthin, and present in marked degree in Ewing's slides, while in Mallory's slides the zymogen was more abundant and the acini practically normal. Warthin also mentioned some dilated and some hypertrophic acini. Where the acini were shrunken the fibrous elements as usual were relatively more prominent, but there was no definite fibrosis found in the acinar tissue. The following features of the islands may be noted. *Number.*—Fewness of islands was men-

1. Removal of the pancreas was the first step in the necropsy, and weighing of it was omitted in the interests of quick fixation.

tioned by Warthin, and they were noticeably few and small in four of the five slides mentioned. In one slide from Mallory islands were fairly abundant and a few were so large and irregular as to suggest hypertrophy. There was nowhere seen any such scarcity as to suggest congenital deficiency of island tissue as the cause of the diabetes. (b) *Fibrous and hyalin changes.*—None such were mentioned by Warthin or Mallory, or observed in the Mallory slides. Ewing's slides showed slight distinct fibrous thickening of the capillary network of all islands, with small hyalin deposits in many of them. (c) *Weichselbaum's "atrophy."*—This was not mentioned by Warthin or Mallory, and the island cells appeared normal in the slides received from Mallory. In Ewing's slides the cells in the great majority of the islands appeared abnormally small, with dense and shrunken cytoplasm and nuclei. This change may have been specific and significant in this instance, along with the slight fibrosis of islands, or may merely have been part of the atrophic appearance of the general parenchyma. (d) *Hydropic degeneration.*—No vacuolation of islands was reported by Warthin, though he mentioned it in tissue from another case sent at the same time. None was found in Mallory's slides or in the great majority of islands in Ewing's slides. But a few islands in the latter were composed almost wholly of swollen cells showing the typical hydropic vacuolation in marked degree.

DISCUSSION

Incidental mention may be made of the treatment and its results. Obviously, the combination of advanced diabetes and advanced tuberculosis was hopeless. The outstanding fact is the marked improvement in the tuberculosis as well as the diabetes under diet treatment, even though this involved undernutrition. In this extreme condition, complete fasting was imposed for a week, followed by very low diets chiefly of protein, so that over a month was occupied in a gradual increase up to 1,200 calories. Gain in strength and resistance to infection was evident during this time. Life was extended for six months. As a lesson for the treatment of milder tuberculosis or prophylaxis against it and other infections in diabetics, the experience indicates that the best success will be attained with restricted diets which control the diabetes, rather than by attempts at over-feeding. It also corroborates other observations that thoroughly treated patients not only live longer but are at the same time more comfortable.

The principal feature of interest is the diabetic heredity. The frequent occurrence of diabetes in certain families is well known, generally as a more or less heavy sprinkling of cases through several generations, but sometimes apparently as a sudden visitation on a single generation out of a clear heredity. Examples are cited in Joslin's and earlier textbooks, and two cases and a bibliography is given in a paper by Foster.[2] The newer ideas of the usual infectious origin of diabetes makes it probable that some cases are strictly accidental and without hereditary influence. Therefore, in addition to the great theoretical interest, there is much practical importance in this point with reference to the frequent question whether diabetics should marry or have chil-

2. Foster, N. B.: Bull. Johns Hopkins Hosp. **23**:54, 1912.

dren. For a fuller discussion and outline of other investigations by one of the present writers, reference may be made to Chapter 8 in Rockefeller Institute Monograph No. 11. The observations in the present case may be classified as they pertain to hereditary characters, the pathology, and infections.

1. *Heredity.*—(a) General conditions: The table shows the ancestry beginning with the grandparents of the present children. In the light of their experience with diabetic symptoms, the mother and older children were positive from diligent inquiries among all their oldest relatives that nothing of the sort had been known in the family up to this time. The first known case was in a brother of the father. The death of the father from apoplexy may indicate nephritis, but this at the age of 61 may carry no great significance. As the family were very ignorant, the occurrence of mild diabetes or other organic diseases among some of the ancestors in their later years is not fully excluded, but the testimony goes far to exclude any severe or obvious diabetes and to establish long life and health as the rule among them. There was no history of inbreeding. It may be added that obesity, sedentary life, high civilization and education, nervous strain and similar reputed causes of diabetes were unknown among them; also their diet was frugal and simple, containing little sugar, fair quantities of cornmeal and wheat flour, adequately balanced with meat and vegetables from their own farms.

(b) Accompanying characters: The grandparents on both sides represented a combination of light and dark individuals. The pure blond character of the maternal grandfather was dominant over the brunet color of his wife. Both these grandparents were notably tall, but the mother of the present children was exceptional among her brothers and sisters for her shortness. The colors of the paternal grandparents blended to produce offspring characterized uniformly by black hair, dark complexions and blue eyes. The first known case of diabetes occurred among this generation of mixed coloring. The father of the present children was taller than the mother, but his family averaged shorter than the mother's family.

Little concerning the heredity of the present children can be elucidated from their height. Four of the diabetic children (No. 2, 3, 4, 5) resembled the father in being blue eyed brunets. One such child (No. 11) has thus far escaped diabetes, according to his glucose test. The illegitimate child was a pure blond like his mother, but nevertheless became diabetic. Two of the present children were classifiable as blonds like their mother except for their hair, which showed a partial influence of the father in being brown. To date, the children having full resemblance to this mother, including her flaxen hair (Nos. 1, 7, 9,

10, 13) have been free from known diabetes. Every rule of association of diabetes with other characters, therefore, has exceptions, though it can be said that all of the legitimate children who most closely resembled their mother have escaped diabetes. Also, in general, the father's influence was most pronounced among the earlier children, and these up to No. 6 (except No. 1, who died at 12 years from a fall) all developed diabetes. The later children showed less influence from the father in general and correspondingly less diabetes. As the father was about ten years older than the mother, there may be a question whether advancing age had anything to do with his loss of dominance.

(c) Unit inheritance: The above record shows certain characters of complexion, etc., sometimes transmitted as units and sometimes more or less blended. It may be inquired whether the diabetic disposition behaved as a mendelian unit or was blended so as to produce varying grades of carbohydrate tolerance. This bears relation to the practical question whether all children of a diabetic family observe precautions in diet or whether some may enjoy the liberty of normal persons. It is clinically well known that some members of diabetic families do indulge in unlimited gluttony and still escape diabetes, but it is not established whether the danger from such practices is greater to them than to other persons. The glucose tolerance tests revealed one case of incipient diabetes in this family (No. 4), and this individual received the benefit of early instructions in dietary care. It is an open question how early in his life the test would have indicated such an abnormality; whether the diabetic tendency was congenital or began with a pancreatitis. Of the two tests taken at the half-hour interval after the dose (Nos. 7 and 9), it is noticeable that both show distinctly high values (0.192 and 0.200 per cent); but general experience by no means justifies the suspicion of diabetes in persons showing such figures when the results in the subsequent samples are normal. If there is any diabetic tendency or need for carbohydrate restriction in any of the children other than No. 4, these tests do not reveal it. Two facts from animal experiments merit consideration in this connection. First, the proportion of pancreas which must be removed to cause diabetes varies from about seven-eighths or nine-tenths in the dog to about four-fifths in the cat; and very large fractions, fully two-thirds in the dog, must be removed to produce any demonstrable lowering of carbohydrate tolerance. The margin of safety in the human pancreas is unknown, but is presumably large, so that possibly the loss of from one-half to two-thirds of its islands or a corresponding functional deficiency might be undetected in tolerance tests and yet be important as narrowing the margin of safety. The second is that in animals the division point between diabetes and its absence is sharp and definite, and may be represented

by only a fraction of a gram of pancreatic tissue. Up to this point, no matter how low the tolerance, the production of diabetes is impossible by carbohydrate excess in any degree or duration. After removal of the additional bit of tissue, though the tolerance may appear little changed, the animal is potentially diabetic and its fate thenceforth is governed by the diet. The deduction from this is that diet may aggravate but never actually produce diabetes; that no matter how narrow the margin of safety, diabetes can result only from some infection or other further injury of the pancreas, and that carbohydrate restriction is unnecessary unless diabetes is already present. In animals, the ready assimilation of sufficiently large quantities of sugar suffices to demonstrate the absence of diabetes and the harmlessness of carbohydrate feeding; but in them the pancreatic islands are normal in character and only artificially reduced in quantity. The pathology of human diabetes as far as now known is against such a simple quantitative explanation and requires the assumption of functional defects in the islands. It is therefore not possible to say with certainty that the normal outcome of a glucose tolerance test proves that the pancreas of an hereditarily predisposed individual can carry a heavy burden on its endocrine function indefinitely without breaking down.

2. *Pathology.*—(a) Methods: Simple methods, namely, Zenker fixation, paraffin sectioning, and staining with eosin and methylene blue or hematoxylin, are sufficient for all purposes except special investigations requiring differentiation of alpha and beta cells in the islands. The reasons why pathologists have generally observed only the structural alterations and missed the finer specific changes described as long ago as 1901 by Weichselbaum,[3] are chiefly two. First is the failure to obtain sufficiently fresh tissue. Immediate necropsy, with removal of the pancreas as the first step, is the best procedure. Though the rate of autolysis varies widely, specimens more than a few hours old are seldom satisfactory. The freshness of animal tissues, where even agonal changes are avoided, is one reason why the changes seen in them are so much more distinct. Second is the failure to study a sufficient number of sections. Specimens should be taken in separate bottles from the different portions of the gland, and a negative report is not justified unless several dozen slides, representing several different blocks from each portion, have been thoroughly searched. The differences found by Bensley[4] even between adjacent areas of normal pancreas are more marked in pathologic material, and the most accurate description of a few slides may be misleading.

3. Weichselbaum, A., and Stengl, E.: Wien. klin. Wchnschr. **14**:968, 1901; **15**:969, 1902. Weichselbaum, A.: Sitzungsber. d. kais. Akad. Wissensch. **119**: 73, 1910; Wien klin. Wchnschr. **24**:153, 1911.

4. Bensley, R. R.: Am. J. Anat. **12**:297, 1911.

(b) Cellular exhaustion: In milder diabetic cases the functional overstrain is seldom rapid and intense enough for positive anatomic demonstration. In severe cases with unchecked symptoms, the hydropic degeneration of Weichselbaum and Stangl is seldom missed in a thorough search of fresh material. Anyone interested can easily convince himself with animal experiments that this change represents anatomic destruction of island cells by functional overstrain. The severest diabetes, if thoroughly controlled by diet, never shows hydropic degeneration, and the strongest argument for thorough treatment is that it actually prevents this form of progressive destruction of islands. Less thorough dietetic control gives corresponding anatomic pictures. This patient had had moderate glycosuria for some weeks before death; accordingly, visible exhaustion of island cells was not widespread but could be found by search.

(c) Structural abnormalities: No structural changes of the pancreatic parenchyma have ever been found strictly specific of diabetes, though fibrosis and hyaline transformation of islands are highly suggestive and in their most pronounced grades must entail diabetes. The variable pictures in the human pancreas can by sufficient care be duplicated in animal experiments, where an acute aseptic inflammation gives rise to diabetes. The production of considerable fibrosis without diabetes is readily comprehensible; but what has not been generally appreciated in clinical pathology is the nearly perfect structural repair which can be attained after an acute pancreatitis has actually caused diabetes. Even though the fibrosis or other visible lesions at autopsy be slight, they may assume much importance as vestiges of a former severe inflammation, or on the other hand as evidence of a low grade chronic toxic injury. Even a normal pancreatic structure with diabetes could receive a rational interpretation through the above experiments, though as a matter of fact, the extensive clinical series on which these generalizations are based has included no diabetic pancreas actually free from signs of infectious or toxic injury. The evidence in the present case is indecisive, because the slight sclerosis of islands might conceivably be due to the toxins of tuberculosis subsequent to the beginning of diabetes. Nevertheless, the findings fall within the terms of a previous statement, that the pathology of hereditary diabetes resembles that of diabetic cases in general.[5] The evidences of inflammatory or toxic injury are the same, and the problem of heredity is not one of direct transmission of diabetes or anatomic lack of islands, but rather of liability to certain forms of pancreatic injury or the consequences of them.

5. Rockefeller Institute Monograph, No 11, Chapter 8.

3. *Infection.*—(a) Theoretical status: The few early suggestions of diabetes as a communicable disease were baseless, and interest and clearness concerning it as the consequence of infectious injury of an endocrine organ may be said to date from the pronouncement of Woodyatt.[6] Syphilis as a cause of diabetes was especially emphasized by Warthin.[6] Cases of diabetes apparently due to acquired syphilis are known to most clinicians, and furnish support for the general conception of the infectious etiology. The clinical evidence for hereditary lues is less definite, but the characteristic pancreatitis of syphilitic fetuses and infants furnishes some presumptive support. Certainly most pancreatitis and most diabetes is not syphilitic. Organisms of the streptococcus group, so strongly stressed by the Rosenow school, are probably responsible for many more cases, but it is not proved that they hold any monopoly. The organisms of pneumonia, mumps, typhoid and other diseases, as well as staphylococci and colon bacilli, appear clinically as causes of diabetogenic lesions. It seems reasonable that many such cases are strictly accidental and without hereditary origin or influence.

(b) General diseases: The apparently sudden occurrence of diabetes and apoplexy in a certain generation, followed by widespread diabetes in the next generation, and especially the transmission through the father to both illegitimate and legitimate offspring, brought this case preeminently under the suspicion of syphilis. Accordingly, this question received attention, and it can be said from clinical and blood studies of the family, clinical and Wassermann examinations (blood and spinal fluid) of the patient, and from the gross necropsy, the microscopy of the tissue, and stains for spirochetes, that syphilis was absent. Malaria, hookworm and pellagra were also considered and excluded. It is conceivable that one or more of the childhood diseases which this patient passed through might have caused pancreatic injury, especially in a predisposed individual, followed by functional deterioration and the outbreak of diabetes years later, but such an idea here is merely speculative.

(c) Local diseases: Owing to the excellent efficiency and cooperation of the various services of the hospital, it was possible to have roentgenograms of the patient's teeth, and special examinations by the dental, eye, ear, nose and throat, genito-urinary and surgical services in addition to the medical service. Except for dental caries and pyorrhea, evidently due to diabetes and neglect, nothing was found which in the opinion of any of the consultants could have served as a focus of infection or intoxication to give rise to the diabetes. The microscopic pathology was discussed above in relation to the etiology through infec-

6. Woodyatt, R. T.: Abstract of Proceedings of Seventh Annual Meeting of American Society for Advancement of Clinical Investigation, 1915, p. 25.

tious or toxic injury of the pancreas, but no reason was found for the susceptibility of this patient or others of his family to such injury. The bile and pancreatic passages were clear, and the localization of the lesions in the islands suggested an origin not through the ducts, but through the blood stream. Two hypotheses might suggest themselves, namely, that the diabetic predisposition might consist merely in a liability to low grade septicemia or toxemia (which would be convenient to explain the association of diabetes, nephritis and other endocrine disorders in different members of a family), or on the other hand that the slight changes in this pancreas were not primary or etiologic, but purely secondary to the tuberculous and mixed infection of the lungs. The chronic lymphadenitis might harmonize with either of these views, neither of which can be disproved in this case; but the negative findings in most of the viscera here, and the numerous cases of diabetes without other diseases, would seem to indicate a special vulnerability of the endocrine pancreatic structures in this family. Rosenow's theory of a specific and heritable lack of resisting power in certain organs against certain micro-organisms would explain such a condition. Some anatomic peculiarities falling under the more orthodox conceptions of heredity, for example, a circulatory apparatus faulty either structurally (in the vascular supply or the position of the organ) or functionally (through the nerve supply) might predispose to infectious or toxic injury, and the latter assumption might revive the old hypothesis of the nervous etiology. It is only possible at present to state the facts of pancreatic damage in hereditary cases and leave the explanation to the future.[7]

SUMMARY AND CONCLUSIONS

1. One of the patients in the diabetic service of this military hospital came of a family in which seven out of fourteen children of one father (one by one woman, thirteen by another woman) were diabetic. In addition to the treatment, clinical and pathologic studies were carried out in the attempt to throw light on the hereditary feature of the condition.

2. The patient when received was in the later stages of diabetes and tuberculosis, with dangerous acidosis, emaciation and weakness. In consequence of a week of fasting and a month of extreme undernutrition, he became able to tolerate diets between 1,500 and 2,000 calories without glycosuria or acidosis, showed improvement in strength and lung symptoms, and lived six months. This result in a case of this severity adds to the evidence that the combination of diabetes and tuberculosis is best treated by a diet which controls the diabetes.

7. Warthin, A. S., and Wilson, U. F.: Am. J. M. Sc. **152**:157, 1916. Warthin, A. S.: The Harvey Lectures **13**: 1917-1918.

3. Clinical examinations of the patient and his family for general or focal infections, including clinical and serological examinations for syphilis, were negative. Glucose tolerance tests afforded an early diagnosis of one of the above-mentioned seven cases of diabetes, but were negative in the mother and remaining children.

4. The gross and microscopic pathologic findings served further to exclude syphilis, and were characteristic of tuberculosis. The pancreas showed changes of two types, namely, occasional hydropic degeneration of islands, which is the result of functional over-strain, and slight fibrosis and hyalin formation in islands, which may indicate infectious or toxic damage as the cause of the diabetes.

5. In general, the diabetic heredity, which apparently came through the father, was manifest in the children who most resembled him in coloring of complexion, eyes and hair, but the rule was not absolute. As far as glucose tolerance tests could decide, the diabetic tendency was inherited as a unit character and the tolerance of the remaining children was apparently normal; but this evidence is not decisive, partly because of the limitations of this test in revealing pancreatic deficiency, and partly because the tendency might consist in a susceptibility to infectious or toxic injury, which might yet appear in the other children if the proper organism gained access. This case conforms to the general rule that signs of infectious or toxic damage are found similarly in hereditary and other cases of diabetes. The reason for the peculiar liability to diabetogenic injuries of the pancreas in certain families is undetermined.

PREVENTION OF SIMPLE GOITER IN MAN

FOURTH PAPER *

DAVID MARINE AND O. P. KIMBALL

CLEVELAND

In previous publications [1] we have outlined the plan of prevention, presented the data of the incidence of thyroid enlargements as determined by annual surveys of all new pupils in the Akron public schools, and the results of the prophylatic use of sodium iodid for nineteen months. The present paper deals with the data obtained at the fourth general examination made October 13-17, 1919, together with summaries and conclusions based on observations extending over a period of thirty months.

ANALYSIS OF THE RECORDS OF NEW PUPILS

The general data of the clinical condition of the thyroid gland are given in Table 1. For comparison and reference the figures for the three previous examinations are also given.

The pupils included in this table are new admissions to all grades from the fifth to the twelfth, inclusive, and presumably had not previously received iodin. The figures in the first line represent the results of the original survey of all girls in grades from the fifth to the twelfth, inclusive. The figures in the second line include (1) incoming fifth grade girls, (2) girls entering grades above the fifth grade, and (3) girls of two schools that accidently lost the records of those not taking the treatment. The figures in the third and fourth lines include (1) incoming fifth grade girls and (2) girls entering grades above the fifth. The progressive increase in the percentage of normal thyroids (43.6, 47.0, 55.4 and 65.4) and the corresponding progressive decrease in the percentage of enlarged thyroids whether taken together (56.4, 53.0, 44.6 and 34.5) or as separate groups (slightly enlarged, moderately enlarged and markedly enlarged) are due to the increasing preponderance of fifth grade girls in the second, third and fourth groups. This is also shown in Table 2, where all new pupils are grouped according to ages. Fifth grade pupils average from 10 to 11 years of age, and approxi-

* From the Department of Experimental Medicine, Western Reserve University.

* Aided by a Grant from the Committee on Therapeutic Research of the Council on Pharmacy and Chemistry of the American Medical Association.

1. Marine, D., and Kimball, O. P.: The Prevention of Simple Goiter in Man, J. Lab. & Clin. Med. **3**:40, 1917. Kimball, O. P., and Marine, D.: The Prevention of Simple Goiter in Man (Second paper), Arch. Int. Med. **22**:41 (July) 1918. Kimball, O. P., Rogoff, J. M., and Marine, D.: The Prevention of Simple Goiter in Man (Third paper), J. A. M. A. **73**:1873 (Dec. 20) 1919.

TABLE 1.—Analysis of the Records of New Pupils

Date Examined	Total Cases Examined	Total New Cases	Normal		Slight Enlargements		Moderate Enlargements		Marked Enlargements		Adenomas	
			Number	Per Cent.	Number	Per Cent.	Number	Per Cent.	Number	Per Cent.	Number	Per Cent.
April 1917.....	3,872	3,872	1,688	43.6	1 931	49.9	246	6.3	7	0.2	39	1.0
November 1917.....	4,415	1,772	831	47.0	820	46.2	121	6.8				
November 1918.....	4.277	1,873	1,037	55.4	779	41.6	53	2.8	4	0.2	6	0.3
October 1919.....	5.520	2,102	1,415	65.4	679	31.4	67	3.1	1	0.05	1	0.05

TABLE 2.—Summary of Age Incidence—New Pupils

Date of Examination	Total New Cases	Age									
		10 - 12		12 - 14		14 - 16		16 - 18		18 - 20	
		Number of Cases	Per Cent.	Number of Cases	Per Cent.	Number of Cases	Per Cent.	Number of Cases	Per Cent.	Number of Cases	Per Cent.
April 1917.....	3,872	945	24.4	1,261	32.6	1,140	29.4	453	11.7	73	1.0
November 1918.....	1,873	766	40.9	590	31.5	406	21.7	94	5.0	17	0.9
October 1919.....	2,102	969	44.8	678	31.4	401	18.6	102	4.7	12	0.5

TABLE 3.—Relation of Age to Thyroid Condition—New Pupils—1917

	Age									
	10 - 12		12 - 14		14 - 16		16 - 18		18 - 20	
	Number of Cases	Per Cent.	Number of Cases	Per Cent.	Number of Cases	Per Cent.	Number of Cases	Per Cent.	Number of Cases	Per Cent.
Normal.....	530	56.1	521	41.3	460	40.3	156	34.4	21	28.8
Slightly enlarged.	394	41.7	680	53.9	578	50.7	235	51.9	44	60.3
Moderately enlarged.....	21	2.2	59	4.7	98	8.6	60	13.2	8	11.0
Markedly enlarged.....	...	....	1	0.1	4	0.3	2	0.4		

TABLE 4.—Relation of Age to Thyroid Condition—New Pupils—1918

	Age									
	10 - 12		12 - 14		14 - 16		16 - 18		18 - 20	
	Number of Cases	Per Cent.	Number of Cases	Per Cent.	Number of Cases	Per Cent.	Number of Cases	Per Cent.	Number of Cases	Per Cent.
Normal.....	491	64.2	295	50.0	214	52.7	39	41.5	9	52.9
Slightly enlarged.	267	34.8	276	46.8	168	41.4	49	52.1	6	35.3
Moderately enlarged.....	8	1.0	19	3.2	24	5.9	6	6.4	2	11.8
Markedly enlarged.....	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

mately 95 per cent. are included in the age group from 10 to 12. Details of the relation of age to the clinical condition of the thyroid are given in Tables 3, 4 and 5.

TABLE 5.—Relation of Age to Thyroid Condition—New Pupils—1919

	Age									
	10 - 12		12 - 14		14 - 16		16 - 18		18 - 20	
	Number of Cases	Per Cent.	Number of Cases	Per Cent.	Number of Cases	Per Cent.	Number of Cases	Per Cent.	Number of Cases	Per Cent.
Normal	743	76.7	419	61.8	199	49.6	88	51.9	7	58.3
Slightly enlarged	215	22.2	239	35.3	170	42.4	43	42.2	5	41.7
Moderately enlarged	11	1.1	20	2.9	31	7.8	6	5.9	0	0.0
Markedly enlarged	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0

TABLE 6.—Analysis of Records of New Pupils—Negroes—1919

	Age					
	10 - 12		12 - 14		14 - 16	
	Number of Cases	Per Cent.	Number of Casec	Per Cent.	Number of Cases	Per Cent.
Normal	5	50.0	7	53.9		
Slightly enlarged	4	40.0	5	38.5	3	75.0
Moderately enlarged	1	10.0	1	7.6	1	25.0

For reference and comparison the original survey of all pupils (April, 1917), is given in Table 3, while in Tables 4 and 5 are given the results of the surveys of new pupils for 1918 and 1919, respectively. It should be emphasized, that in the 1917 examination, 43.9 per cent. of the girls in the 10-12 years age group had enlarged thyroids; that in the 1918 examination 35.8 per cent. had enlarged thyroids; and that in the 1919 examination 23.2 per cent. had thyroid enlargements. This is important from the standpoint of the age at which the phophylactic treatment should be started. When this work was begun, no data of this kind were available, and the fifth grade was arbitrarily chosen as the lower limit, because our limited facilities made it necessary to confine our efforts to what seemed to be the most important age periods. We have seen only forty instances of moderately enlarged glands and no instance of marked enlargement in the 10-12 years age group, and as very striking therapeutic effects are seen in these slight hyperplasias it makes little difference in the ultimate result. If, however, one had to depend entirely on prevention it would be necessary to begin at an earlier age.

There appears to be no noteworthy difference in the incidence of thyroid enlargements between white and colored children. The data are, however, insufficient for any definite conclusion. The data on the twenty-seven colored children are given in Table 6.

EFFECT OF PROPHYLACTIC TREATMENT

The prophylactic treatment as carried out for the past two years consists of the administration of 2 gm. sodium iodid, given in 0.2 gm. doses daily, for ten consecutive school days, repeated each spring and autumn. The general data of those pupils not taking the treatment are given in Table 7, and of those taking the treatment in Table 8. Only pupils with two or more consecutive examinations have been included in the tabulations. A considerable number of pupils, both taking and not taking the treatment, have been omitted because they missed one examination, although otherwise their records were complete. Two thousand, three hundred and five pupils are included in the tabulation

TABLE 7.—RECORD OF PUPILS NOT TAKING PROPHYLACTIC TREATMENT

Time Under Observation, Mos.	Normal				Slightly Enlarged						Moderately Enlarged					
	Unaltered		Increased		Unaltered		Increased		Decreased		Unaltered		Increased		Decreased	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
6	47	50.0	47	50.0	98	69.4	36	26.9	5	3.7	16	69.6	7	30.4	0	0.0
12	420	75.5	136	24.5	251	70.3	35	9.8	71	19.9	17	65.4	8	30.8	1	3.8
18	103	65.2	55	34.8	108	74.5	18	12.3	19	13.1	11	57.9	3	15.8	5	26.3
24	135	76.7	41	23.3	106	79.7	8	6.0	19	14.3	9	60.0	3	20.0	3	20.0
30	205	75.1	68	24.9	140	73.7	30	15.8	20	10.5	4	66.7	0	0.0	2	33.3

of those not taking treatment, and 2,190 in the tabulation of those taking treatment. Further, it was necessary to tabulate the results with reference to the length of time under observation. As the prophylactic treatment was given at intervals of six months, we have used this interval as the unit and grouped the pupils according to the periods under observation, 6, 12, 18, 24 and 30 months respectively. Only the results of three groups (normals, slightly enlarged, and moderately enlarged) are included because the fourth group (markedly enlarged) is too small. A comparison of the two tables brings out striking differences between those not taking and those taking iodin. These differences are manifested both in *prevention* of enlargement and in a *decrease* in the size of existing enlargements, i.e., therapeutic effect.

Prevention.—This effect is shown in the columns marked "unchanged" and "increased." Taking the totals for the five six month periods (Table 9) the following results were obtained. Of those that were normal at the first examination and did not take iodin, 347, or 27.6 per cent., have enlarged thyroids, while of those that were normal at the first examination and took iodin as outlined, two, or 0.2 per cent.,

have enlarged thyroids. These two instances of enlargement were investigated. The first pupil, M. T., age 16, had her thyroid examined and classified as normal May 2, 1917, Oct. 17, 1918 and Dec. 3, 1918. At the examination Oct. 15, 1919, it was classified as slightly enlarged. This girl had taken 2 gm of sodium iodid during each of the five possible periods, May, 1917, November, 1917, May, 1918, December, 1918 and May, 1919. A special examination was made Jan. 13, 1920. The enlargement of the thyroid was verified. The enlargement was acquired as opposed to congenital, as shown by the absence of a pyramidal process or thyroglossal tract. The tonsils were markedly enlarged, nearly meeting in the midline when the mouth was widely opened.

TABLE 8.—Record of Pupils Taking Prophylactic Treatment

Time Under Observation, Mos.	Normal				Slightly Enlarged						Moderately Enlarged					
	Unaltered		Increased		Unaltered		Increased		Decreased		Unaltered		Increased		Decreased	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
6	17	94.4	1	5.6	54	69.2	1	1.3	23	29.5	9	81.8	0	0.0	2	18.2
12	344	99.7	1	0.3	187	45.5	0	0.0	224	54.5	10	23.8	0	0.0	32	76.2
18	73	100.0	0	0.0	72	52.3	1	0.7	64	46.7	7	28.0	0	0.0	18	72.0
24	184	100.0	0	0.0	72	37.9	1	0.5	117	61.6	2	7.7	0	0.0	24	92.3
30	288	100.0	0	0.0	92	28.5	0	0.0	231	71.5	1	2.6	0	0.0	38	97.4

TABLE 9.—Summary—Records of Pupils Taking and Not Taking Prophylactic Treatment

	Taking		Not Taking	
	Totals	Per Cent.	Totals	Per Cent.
Normal:				
Unchanged	906	99.8	910	72.4
Increased	2	0.2	347	27.6
Slightly Enlarged:				
Unchanged	477	41.9	688	72.8
Increased	2	0.3	127	13.3
Decreased	659	57.8	134	13.9
Moderately Enlarged:				
Unchanged	29	20.3	57	64.0
Increased	0	0.0	21	23.6
Decreased	114	79.7	11	12.4
Total	2,190	....	2,305	

They were abnormally hyperemic, and on direct questioning the pupil stated she was subject to recurrent tonsillitis. There was also slight enlargement of the lymphoid tissue at the base of the tongue and in the nasopharynx. The general impression was that of a neurotic individual with general lymphoid hyperplasia.

The second girl, aged 15, had her thyroid first examined and classified as normal Nov. 27, 1918. At the examination Oct. 16, 1919, it was classified as slightly enlarged. This girl had taken 2 gm. sodium iodid during each of the two available periods, November, 1918 and May, 1919. A special examination was made Jan. 13, 1920, and the thyroid

enlargement was verified. Careful inspection revealed the presence of Hutchinson teeth, depressed nasal arch and interstitial keratitis. We considered the case one of neglected congenital syphilis.

Passing to Group 2, or those classified as having slightly enlarged thyroids at the first examination, it is seen among those not taking the prescribed treatment that 127, or 13.3 per cent., underwent further enlargement, while of those taking the prescribed treatment, three, or 0.3 per cent., underwent further enlargement. Two of these three pupils were again examined Jan. 13, 1920. One, R. R., aged 14, was examined May 2, 1917, Oct. 12, 1917 and Nov. 26, 1918, and the thyroid classified as slightly enlarged, and at the examination Oct. 16, 1919 the gland was classified as moderately enlarged. This girl had taken the prescribed treatment only during the last three available periods, May, 1918, November, 1918 and May, 1919. A special examination was made Jan. 13, 1920 and the thyroid enlargement verified. In this case also the tonsils were enlarged and the seat of recurrent infections. The second case, V. S., aged 11, was examined Oct. 22, 1917 and Nov. 27, 1918 and the thyroid classified as slightly enlarged. At the third examination, Oct. 16, 1919, it was classified as moderately enlarged and the special examination Jan. 13, 1920, verified this finding. This girl had taken the prescribed treatment during the four available periods, November, 1917, May, 1918, December, 1918, and May, 1919. Superficial inspection failed to reveal the existence of any associated pathologic condition as was found in each of the first three cases mentioned. The fifth girl was not present for the special examination. These five cases are the only instances out of 2,190 pupils taking iodin that showed enlargement. For the group with slightly enlarged thyroids taking iodin, 447, or 41.9 per cent., remained unchanged, while of those not taking iodin, 698, or 72.8 per cent., remained unchanged.

Passing to the third group, or those classified as having moderately enlarged thyroids at the first examination, it is seen that of those taking iodin, twenty-nine, or 20.3 per cent., remained unchanged, while of those not taking iodin, fifty-seven, or 64.0 per cent., remained unchanged; of those taking iodin none increased, while of those not taking it, twenty-one, or 23.6 per cent., increased.

Curative or Therapeutic Effect.—Although of secondary importance, the results are just as striking as those above described under prevention. These results are shown in the column marked "decreased." Of those pupils whose thyroids were classified as slightly enlarged at the first examination, and who took iodin, 659, or 57.8 per cent., definitely decreased in size, while of those not taking the prescribed treatment, 134, or 13.9 per cent., decreased. Passing to the group

whose thyroids were classified as moderately enlarged at the first examination, 114, or 79.7 per cent., of those taking iodin showed definite decreases. In some the decrease in size was most striking and hardly to be believed had we not had actual measurements and descriptions of the condition previously. The reduction in several cases was as marked as one sees in the thyroid enlargement of young dogs, sheep or cattle following the use of iodin. It means that with similar anatomic conditions, i.e., uncomplicated hyperplasias of the thyroids, the degree of reaction is similar. Ordinarily, one does not obtain the striking therapeutic effect on human thyroid enlargements that is seen in animals. This, as pointed out in previous papers, is due, in large part, to the duration of the enlargement, the presence of adenomas, cysts, degenerations, hemorrhage, etc., which are common in all long standing human goiters, while very uncommon in the lower animals at the ages when these animals are usually observed. The therapeutic effect is a very

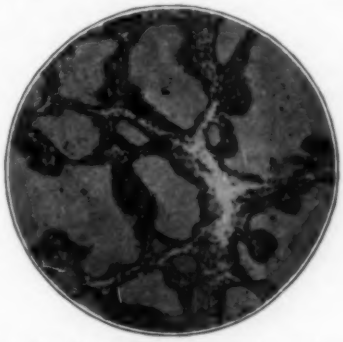


Fig. 1.—Moderate active hyperplasia; control specimen removed ten days after beginning administration of iodin (D—185a).

important supplement to prevention and makes it possible to begin prophylactic treatment in older pupils with the same practical result than would otherwise be possible.

DISCUSSION

Our observations on the prevention of simple goiter in man have extended over a period of thirty months. The disease is as easily prevented in man as in fish or in domestic animals.

Of 2,190 pupils taking 2 gm. sodium iodid twice yearly, five have shown enlargement of the thyroid, while of 2,305 pupils not taking the prophylactic, 495 have shown enlargement of the thyroid. Of 1,182 pupils with thyroid enlargement at the first examination and who took the prophylactic, 773 thyroids have deceased in size, while of 1,048 pupils with thyroid enlargement at the first examination and who did not

take the prophylactic, 145 thyroids have decreased in size. These figures demonstrate in a striking manner both the preventive and the therapeutic effects. There is an error in the above figures in that many pupils listed as not taking iodin have taken iodin in one or another form outside the school jurisdiction. No attempt has been made to detect or estimate this error.

In the practical application of the preventive treatment, one must keep in mind the three periods when simple thyroid enlargements most commonly occur, viz., (1) fetal, (2) adolescence and (3) pregnancy.

(1) Prevention of goiter in mother and fetus is as simple as that occurring during adolescence. Practically, it would seem that it is a charge or responsibility of individual members of the medical profession supplemented with public education.

(2) The prevention of goiter of adolescence, on the other hand, should be a public health measure under state, county or municipal

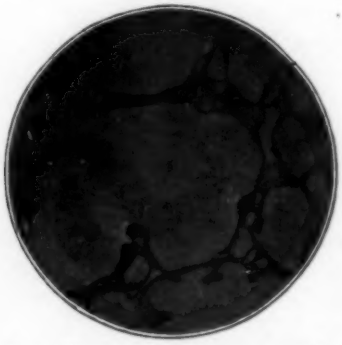


Fig. 2.—Same gland as Figure 1; specimen removed forty-four days after beginning administration of iodin.

control. The existing systems of organization of the schools, public and private, is sufficient to handle all the details without additional aid or expense. Education of the pupils would be combined with the actual administration so that after leaving school they could continue the treatment, if necessary. Physicians in industrial medicine could render an important service in this field. Thyroid enlargement is approximately six times as frequent in girls as in boys. It is a social economic question each community must decide whether it will include both sexes. Likewise, as to the age of beginning and stopping the use of iodin. In this climate probably the maximum of prevention, coupled with the minimum of effort, would be obtained by giving it between the ages of 11 and 17 years. As applied to our schools it would mean beginning with the fifth grade.

Manner and Form of Administration.—As previously stated, iodin is taken up by the thyroid gland when given by mouth, by inhalation, or by external application. Weith [2] reports favorable therapeutic effects from inhalation of iodin as carried out by suspending a wide mouthed bottle containing a 10 per cent. tincture of iodin in the school room. Waste and lack of control of amounts taken are the most obvious objections. Similar objections hold in case of external application. Some form of oral administration seems most practical and economical. The addition of iodin or a salt of iodin to the water supply as we have done in preventing goiter in fish might be considered. There are obvious objections to such a plan. It would entail enormous waste. It is applicable only when there are installations, i. e., in towns and cities, and depending on the chemical impurities in water interactions might throw out the iodin. The most feasible oral method would seem to be the individual administration of definite small amounts, either in solution or as tablets. The cheapest salt, sodium iodid, could be given in either form. Manufacturing pharmacists state that sodium iodid could be prepared very cheaply in tablet form protected from the action of water and light. For private use, the well known U.S.P. preparations, syrup of ferrous iodid and syrup of hydriodic acid are excellent.

Amounts of Iodin to be Used.—An ounce of syrup of ferrous iodid or hydriodic acid given over a period of from two to three weeks and repeated twice yearly would seem ample. As a public health measure, we have used 2 gm. of sodium iodid given over a period of two weeks and repeated twice yearly. This dosage has prevented enlargement of the thyroid in more than 99 per cent. of the children in this mildly goiterous district. It is our opinion that much smaller amounts would suffice for healthy children and healthy pregnant women, provided the period of taking was prolonged, i. e., 1 gm. sodium iodid distributed over a month would accomplish as good thyroid effects as 2 gm. given over a period of two weeks.

The prevention of thyroid enlargement in individuals with other diseases or residing in extremely goiterous districts, as in some glacial valleys of Alaska and British Columbia; certain districts in the Alps and Himalayas, might require larger amounts of iodin for normals than above indicated. Our data of the clinical condition of four of the five cases that enlarged during the administration of 2 gm. of sodium iodid, twice yearly, suggest that in infections (chronic catarrhal or suppurative tuberculosis, syphilis, etc.) and possibly also in conditions like chlorosis, osteomalacia, lymphatism and exophthalmic goiter, such amounts might not control the thyroid growth. In such conditions there

2. Weith: Goiter and Iodin in the School, Cor.-Bl. f. schweiz. Aerzte **49**: 1474, 1919.

may be a greatly increased demand for the thyroid hormone or the organism's ability to store iodin in the thyroid may be impaired. There is a great deal of clinical evidence for the first view and none at present in support of the second.

Effect of Iodin on the Thyroid Gland.—This is manifested in two ways (1) on the iodin store and (2) on the histologic condition. Both of these effects have been fully described in previous papers.[3]

Effect on the Store: If the thyroid gland is not saturated with iodin (i. e., contains less than 4 mg. per gm. of dried gland) it is taken up readily by the cells following its administration in any form and in any manner thus far studied. An increase in the iodin content of thyroid may be demonstrated in a few seconds following the injection of a soluble salt into the circulation.[4] Iodin thus taken up is held by the cells until elaborated into the physiologically active hormone, when any

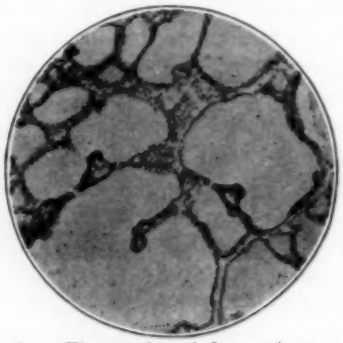


Fig. 3.—Same gland as Figures 1 and 2; specimen removed seventy-eight days after beginning administration of iodin. Total amount of iodin given, 90 mg.

excess is excreted into the follicular spaces and stored in the so-called colloid. Two factors then are concerned in the storage of iodin in the thyroid: (a) the capacity of the gland cells to take up and elaborate the

3. Marine, D.: On the Occurrence and Physiological Nature of Glandular Hyperplasia of the Thyroid (Dog and Sheep) Together with Remarks on Important Clinical Human Problems, Bull. Johns Hopkins Hosp. **18**:359, 1907. Marine, D., and Lenhart, C. H.: Colloid Glands (Goiters): Their Etiology and Physiological Significance, Bull. Johns Hopkins Hosp. **20**:131, 1909. Marine, D., and Lenhart, C. H.: Effects of the Administration or the Withholding of Iodin Containing Compounds in Normal, Colloid or Actively Hyperplastic Thyroids of Dogs, Arch. Int. Med. **4**:253, 1909. Marine, D.: Quantitative Studies on the in vivo Absorption of Iodin by Dogs' Thyroid Glands, J. Biol. Chem. **22**:547, 1915.

4. Marine, D., and Rogoff, J. M.: The Absorption of Potassium Iodid by the Thyroid Gland in vivo Following Its Intravenous Injections in Constant Amounts, J. Pharm. & Exper. Therap. **8**:439, 1916.

hormone and (b) the capacity of the colloid material to store the product. It is evident, then, that to obtain maximum thyroid effects from a minimum amount of iodin, it should be administered in amounts not to exceed the capacity of the cells at any given time to handle it. As has been shown, the elaboration of the hormone proceeds slowly [5] in the most active thyroids. Also when one recalls that from 4 to 5 mg. of iodin per gm. of dried gland, or from 25 to 30 mg., is the total storage capacity of a normal thyroid, it is clear that small amounts of iodin (a few mg.) given daily for a long period of time (a month or more) would produce optimum thyroid effects. In the school work, a compromise was found necessary, increased amounts and decreased time of administration.

Effect on Histology of the Thyroid: It has been shown that the minimum amount of iodin store necessary to maintain normal or quiescent thyroid structure is quite constant for mammals.[6] In the dog, sheep, human and pig thyroid it is approximately 1 mg. per gm. of dried gland, and immediately the percentage is reduced below the minimum, hypertrophic and hyperplastic changes begin and continue until the store of iodin has again been raised above the minimum requirements, when involution takes place. This cycle may be repeated many times in the same individual under natural or experimentally controlled conditions. In young dogs, with active hyperplasia, involution is usually complete in from fourteen to twenty-one days after beginning the administration of iodin. The histologic features of this involution have been described in detail in other papers, but for reference three microphotographs illustrating it are reproduced (Figs. 1, 2 and 3).

Untoward Effects.—No obvious case of exophthalmic goiter has developed, although such cases have been carefully looked for. An occasional instance of iodin idiosyncrasy (iodism), amounting to less than 0.5 per cent. of the cases, was noted. Most of the cases were very mild and the girls did not stop the treatment. As an untoward effect it is negligible.

SUMMARY.

Observations on the prevention of simple goiter in man on a large scale have extended over a period of thirty months. The results show that it may be prevented very simply and cheaply in normal individuals. While thyroid enlargements of adolescence are more common, they are

5. Marine, D., and Rogoff, J. M.: How Rapidly Does the Intact Thyroid Gland Elaborate Its Specific Iodin Containing Hormone? J. Pharm. & Exper. Therap. **9**:1, 1916.

6. Marine, D., and Williams, W. W.: Relation of Iodin to the Structure of the Thyroid Gland, Arch. Int. Med. **1**:349, 1908. Marine, D., and Lenhart, C. H.: Further Observations on the Relation of Iodin to the Structure of the Thyroid Gland in the Sheep, Dog, Hog and Ox, Arch. Int. Med. **3**:66, 1909

not more important than those occurring in mother and fetus. Prevention of adolescent goiter is properly a public health problem, while the prevention of fetal and maternal thyroid enlargements is largely a responsibility of individual physicians. The presence of pathologic conditions may modify the result of the prophylactic treatment in individual cases. While such instances are rare they are important and merit detailed reports.

FURTHER OBSERVATIONS ON THE T WAVE OF THE ELECTROCARDIOGRAM OF THE DOG FOLLOWING THE LIGATION OF THE CORONARY ARTERIES *

FRED M. SMITH, M.D.
CHICAGO

In a former communication [1] it was stated that the T wave of the electrocardiogram of the dog was a marked negative phase on the day following the ligation of branches of the left coronary arteries. This wave remained negative for a period of three to five days and then gradually became positive. The work embodied in this report was undertaken to further these observations and, if possible, inquire into the cause of the negative T wave.

The anesthetic, artificial respiration and the method of exposing the heart were the same as employed in the former work. Electrocardiograms were taken daily of those dogs that survived the operation. On the second or third day following the operation they were anesthetized and the heart was again exposed. The movement of the heart was noted, especially that portion in which the blood supply had been disturbed.

RESULTS OF LIGATION OF THE CORONARY ARTERIES

In twenty dogs various branches of the ramus descendens and of the circumflexus sinistra were ligated. Sixteen survived the operation. Fourteen of these, on the day following the operation, gave an electrocardiogram in which the T wave was markedly negative (Fig. 1). In one of the exceptions the necropsy showed that the lumen of the ligated vessel had not been completely occluded. In the other case, collateral circulation had been established to a remarkable degree.

The negative phase of the T wave was greatest in those dogs in which the blood supply to the apex was most disturbed, as when two or more branches of the ramus descendens and circumflex sinistra, that supplies this area, were ligated. Individual differences seemed to vary with the amount of collateral circulation that was established.

---

* From the Medical Department of Rush Medical College and Presbyterian Hospital.

* This investigation was aided by funds given by Mrs. C. H. McCormick and Mr. R. T. Crane, Jr.

1. Smith, Fred M.: The Ligation of Coronary Arteries with Electrocardiograph Study, Arch. Int. Med. **22**:8 (July) 1918.

The striking features of the movement of the normal ventricles of the dog are a shortening of all the diameters and a tilting of the apex to the right during the systolic period. A satisfactory method of observing these movements was to place a superficial row of sutures at regularly spaced intervals on the longitudinal and transverse diameters in the form of a cross over the area chosen for observation. Those hearts in which branches of the left coronary artery had been ligated, showed a decrease in the activity of that portion in which the circula-

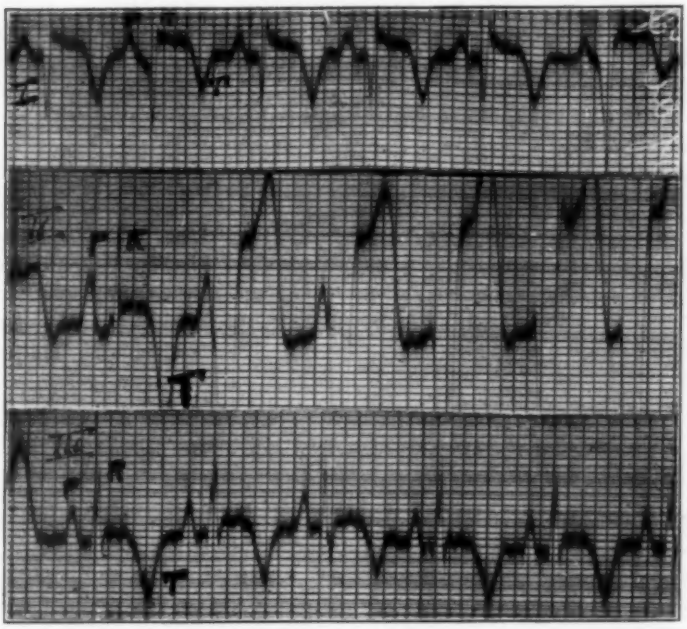


Fig. 1.—Leads I, II and III of a dog one day following ligation of branches of the left coronary arteries. The T wave is a negative phase.

tion had been disturbed. During the systolic period none of the diameters were shortened as in the normal contracting cardiac tissue. The degree of lessened activity and the extent of the area to which it was confined varied in individual cases with the size and number of vessels ligated and the amount of collateral circulation that was later established.

In eight dogs the right coronary artery was ligated. Three died the following night. In the remaining five a necropsy was performed on the second or third day after death. In no instance did the ligation of this artery appreciably affect the direction of the T wave.

THE EFFECT OF COOLING AND HEATING VARIOUS AREAS OF THE VENTRICLES

In experiments on the normal heart of the dog, the effects on the T wave of the applications of heat and cold to various areas were observed. The heat was applied by means of small pledgets of cotton which had been soaked in water of 120 F. temperature. Areas of the heart were cooled by the application of pledgets of cotton which had been soaked in ice water or by the application of a pencil of ice. More satisfactory results were obtained by the use of ethyl chlorid.

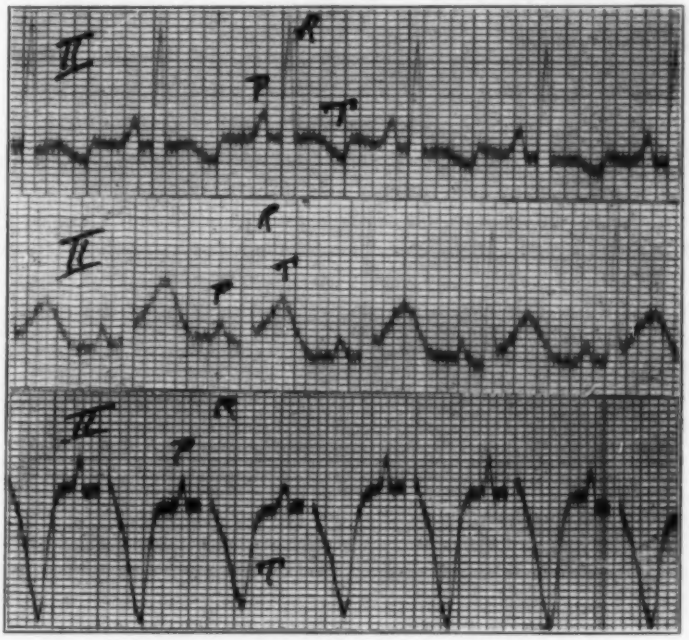


Fig. 2.—Lead II. Top: control.
Middle: Taken following the application of heat to the apex. The T wave has changed to a positive phase.
Bottom: Taken following the application of ethyl chlorid to the apex. The T wave is sharply negative.

By means of this agent, the cooling could be more definitely localized on the desired areas of the heart and was employed in most of the experiments instead of the ice or ice water.

The cooling of the apex by either of these agents produced a negative T wave similar in character to that following the ligation of the branches of the left coronary artery (Fig. 2). When the middle

anterior surface of the left ventricle was cooled, this wave was much less negative and cold applications to the anterior basal surface had no effect. The cooling of various areas of the right ventricle did not change the electrocardiogram, except when applied to the basal region, in which case the height of the T wave was increased in some instances. The application of heat had the opposite effect to that of cold. The greatest change was produced when the heat was applied to the apex. The "T" became markedly positive. A negative condition of this wave, produced by cooling, could readily be changed to a positive by the application of heat. There was a decrease in the activity of that portion of the heart that was cooled. This was most marked when ethyl chlorid was used.

THE EFFECTS OF THE INJECTION OF BICHLORID OF MERCURY AND NITRIC ACID

The attempt was made to damage isolated areas of the myocardium by mercuric bichlorid (1:1,000) and nitric acid. These substances were injected into the region of the apex by means of a Luer syringe and a small hypodermic needle. The changes produced in the electrocardiogram by these agents were similar. The first effect was an increase in the height of the T wave. Later the R and T wave became fused into one. In one instance, following the injection of nitric acid, the R wave became smaller. Because of the difficulty of limiting the effects of these caustics to definite areas of the cardiac muscle this method was discontinued after four experiments.

COMMENT

Phonocardiograms show that the T wave appears just before the second cardiac tone. It, therefore, may be regarded as representing the end of the systolic period of the ventricles. The most generally accepted interpretation of this wave is that it is produced by the final activity of the base of the ventricles. This conception is based in the main on the views of the following investigators. Burden-Sanderson and Page,[2] in 1880 and 1883, studied the electrical reaction of the ventricles of the frog and tortoise by means of the capillary electrometer. They showed that when heat was applied to the muscle in the region of one pole, the excitation period in this area was shortened. In 1892, Bayliss and Starling[3] made similar observations on the heart of mammals. They concluded that the final ventricular variation was produced by a prolongation of the excitation at the base

2. Quoted from Mines.[1]
3. Bayliss and Starling: Internat. Monatschr. f. Anat. u. Physiol. 9:256.

over that at the apex. Later Gotch [4] employed similar methods. He agreed with Bayliss and Starling that the T wave was produced by the final negativity at the base. He, however, concluded that this late condition at the base was due to the return of the excitation from the apex rather than a prolongation of the excitation at the base over that at the apex, as held by the two former investigators. Gotch worked on the supposition that the heart develops from the primitive cardiac tube in which the contraction wave travels from the venous to the arterial end. His conclusions were based on experiments in which he showed that the area in the vicinity of the aorta became electronegative later than did other points on or away from the base of the ventricles.

Einthoven,[5] and also Krause and Nicolai,[6] agree with the former investigators that the final negativity at the base of the ventricles is responsible for the T wave. They also differ as to the manner in which this late negativity is produced. In this respect Einthoven seems inclined toward the conception of Bayliss and Starling, while Krause and Nicolai possibly agree more with the interpretation of Gotch.

Mines [7] has shown that the T wave of the frog can be changed to a marked positive phase by warming the apex. MacLeod [8] considers the production of a positive T wave in the frog from that which is normally slightly negative, by hurrying up the contracting process at the apex by heat, as convincing evidence in favor of the prevailing interpretation of the last ventricular phase of the electrocardiogram.

Samajloff,[9] and also Dale and Mines,[10] have studied the changes produced in the electrocardiogram of the frog by the stimulation of the sympathetic and vagus nerves. They state that stimulation of the sympathetic usually increases the height of the T wave, while stimulation of the vagus changes it to a sharp negative phase. Dale and Mines concluded that vagus stimulation caused the excitation to last relatively longer at the apex, while stimulation of the sympathetic increases the duration at the base.

---

4. Gotch, F.: The Succession of Events in the Contracting Ventricles as Shown by Electrometer Records (Tortoise and Rabbits), Heart **1**:235, 1909; also Proc. Roy. Soc. **79**: B, p. 273.

5. Einthoven: Arch. Internat. de Physiol. **4**:132, 1906; Arch. f. d. Ges. Physiol. **122**:517, 1908.

6. Krause and Nicolai: Das Elektrokardiogram des Gesunden und Kranken Menschen, Leipzig, 1910.

7. Mines, G. R.: On Functional Analysis by the Action of Electrolytes, J. Physiol. **46**:188, 1913.

8. Macleod: Physiology and Biochemistry, C. V. Mosby & Co., 1918.

9. Samajloff: Quoted from Dale and Mines.[10]

10. Dale, Dorothy and Mines, G. R.: The Influence of Nerve Stimulation on the Electrocardiogram, J. Physiol. **46**:319, 1913.

Hoffmann,[11] and Eyster and Meek,[12] differ somewhat from the opinions that have hitherto been expressed. They interpret the electrocardiogram as being the expression of two processes occurring in the heart muscle, the excitation and the contraction of the muscle. They consider the R wave to be the manifestation of the passage of the stimulus over the bundle of His and its ramifications to the papillary muscles and the T wave, the resultant of the contraction of the ventricles. Even though they differ in this respect, Eyster and Meek state that one of the important factors in determining the size and direction of the T wave is the relative degree of contraction in the base and apical regions of the ventricles.

On the basis of the prevailing conception of the cause of the T wave the most plausible explanation of our results is that the negative phase was produced by the prolongation of the excitation at the damaged apex over that of the basal portion of ventricles. The marked negative T wave on the day following the ligation of branches of the left coronary artery, especially those that supply the apex, is presumably explained on the same grounds, as the negative phase following the cooling of the apex. In the latter instance this change in the T wave subsided soon after the cooling agent was withdrawn. In the former, however, it lasted from three to five days. After this time a certain degree of collateral circulation becomes established, fibrous tissue cells begin to appear in the area of disturbed circulation, and those factors that delay the excitation no longer exist. In our experiments the size and direction assumed by the T wave were most influenced by altering the condition of the apex. This can be better understood by assuming the apex to be the lower pole of the heart. On this basis, the T wave should be influenced in the opposite manner by adopting similar measures at the base of the ventricles. In conformity to this notion, there was some increase in the size of the T wave when the base of the right ventricle was frozen with ethyl chlorid in some of the experiments. These results agree with those obtained by Eppinger and Rothberger[13] who employed similar methods. The fact that those measures which produced striking effects on the T wave when applied to the apex do not have the proportional opposite effect when applied to the base may be due to a more definite localization of the lower pole at the apex than the upper pole at the base.

---

11. Hoffmann: Quoted from Eyster and Meek.[12]

12. Eyster, J. A. E., and Meek, W. J.: The Interpretation of the Normal Electrocardiogram, a Critical and Experimental Study, Arch. Int. Med. **11**: 204 (Feb.) 1913.

13. Eppinger and Rothberger: Quoted from Eyster and Meek.[12]

CONCLUSIONS

1. In twenty dogs two or more branches of the ramus descendens and circumflex sinistra were ligated. Sixteen survived the operation. Fourteen of these gave an electrocardiogram on the following day in which the T wave was a sharp negative phase. The two exceptions were explained at the necropsy. The size that the T wave assumed in the opposite direction varied with the amount of disturbed circulation at the apex.

2. In eight dogs the right coronary artery was ligated. In five of these electrocardiograph studies were made on the day following the operation. The T wave was not appreciably affected by the ligation of this artery.

3. The application of cold had the most marked effect when applied to the apex. A negative phase always resulted. When the middle anterior surface of the left ventricle was cooled the T wave was less negative, and cold applications to the anterior basal surface produced no change. The cooling of various areas of the right ventricle did not affect the T wave, except when applied to the basal region, in which case the height was increased in some instances. When heat was applied the opposite results were obtained.

4. The direction that the T wave assumed in these experiments can best be explained on the prevailing conception that it is produced by the final activity of the base, and that the measures adopted either prolonged or delayed the activity at the apex.

It is a great pleasure to acknowledge my indebtedness to Dr. James B. Herrick for his suggestions.

SEQUENCE AND ARRANGEMENT OF PALLOR AND REDNESS IN IRRITATED SKIN OF NORMAL AND DERMOGRAPHIC INDIVIDUALS

LEWIS B. BIBB, M.D. (LITTLE ROCK, ARK.)
First Lieutenant M. C., U. S. Army
FORT LOGAN H. ROOTS, ARK.

The interesting succession of colors which characterizes dermographism has been studied by Jankowsy, Lapinsky and others. It is well known that the lesions not only undergo alternations of pallor and redness, but that two or more zones of alternating pallor and redness may be observed simultaneously. A case of Raynaud's disease, presenting similar zones and undergoing similar alternations of color, suggested that these changes might be of fundamental importance and widespread occurrence. The following series of experiments was accordingly planned, with a view to ascertaining whether the zones of pallor and redness, or the occurrence of pallor followed by redness, were also characteristic of lesions produced by various other irritants.

The irritants used were mechanical, thermal, chemical and electric. Mechanical irritation or injury was provoked by stroking the skin with a blunt object, such as a toothpick; by scratching the skin with a needle; and by pinching a bit of skin between the jaws of a hemostat. Thermal injury was provoked by applying a hot iron or a heated glass rod to the skin. Mosquito bites afforded the opportunity to observe the effects of chemical irritants, and the electrolytic needle with galvanic current constituted the injurious electrical agent. Finally, carbon dioxid snow was applied for producing lesions due to lowered temperature.

The toothpick was applied to the skin of three dermographic and two hundred normal persons. The needle scratch was applied to eighteen individuals. The carbon dioxid snow was applied to the skin of two normal persons and one person suffering from Raynaud's disease. The electrolytic needle was applied to one dermographic person and to three normal persons. One person who was burned accidentally afforded opportunity to record the stages of a burn; three persons who were bitten by mosquitoes furnished the basis of observations on poisoned wounds. Finally, an experimental animal (dog) was subjected to all the varieties of injury just mentioned and to one other, namely, pinching or crushing with a hemostat.

There was a striking similarity between the lesions produced by the various means enumerated, in that they all tended toward wheal formation. Virtually all lesions showed pallor over the contact spot immediately after the injury, and the pale spot usually became sur-

rounded by a peripheral red zone within a few minutes. Within from two to thirty minutes, the pale contact spot became pink, and in some instances the peripheral red zone also underwent a reversion of color, becoming pale.

The development of edema usually proceeded at a rate which produced visible elevation by the end of a few minutes, and this swelling was, in certain instances, associated with a secondary pallor at the contact spot. This was particularly true of dermographic lesions and lesions produced on normal skin by the application of carbon dioxid snow.

The carbon dioxid snow was applied in the form of a truncate crayon 2 cm. in diameter. The lesions produced by this agent were typical wheals, but showed as many as four color zones at certain moments.

It is well known, that the wheal is the lesion characteristic of dermographism, and that formation of wheals constitutes the usual reaction of normal skin toward insect bites. This series of experiments tends to show that dermographic skin reacts like normal skin, and that both normal and dermographic skin react similarly toward mechanical and other forms of trauma.

Chambard and certain other authors have reported failure in the attempt to provoke dermographic lesions by electrical, chemical and thermal stimuli. A careful analysis of the dermographic lesion will show, however, that even the mechanical means must be applied in a certain manner before the formation of wheals is achieved. For instance, a flat-pointed tooth-pick one-eight inch wide, drawn with moderate friction across dermographic skin, will cause an edematous streak along each edge of the path described, but the intermediate space does not become elevated until after the two margins coalesce in the center. Moreover, the cuticle of dermographic skin can be removed with "00" sandpaper without causing a wheal. These facts indicate that in dermographism the wheal is the result of mechanical forces acting according to a certain arrangement, extending over a certain area, and reaching a certain depth.

The fact that electrical, chemical and thermal stimuli have been applied to dermographic skin by some investigators without provoking wheals, can be explained on the ground that the extent and depth of tissue affected by the stimuli was probably dissimilar to that affected by the usual friction stroke, while, on the other hand, the occurrence of urticarial wheals as a result of soluble poisons circulating in the blood, lowered temperature, affecting the entire body surface, instrumentation of the urethra, and even intense emotion, appears to establish the hypothesis that there is an inherent tendency in the skin to react in one stereotyped fashion to all forms of irritant.

CONCLUSIONS

1. The reactions observed in dermographism seem to be entirely analogous to those observed in normal skin, differing only in degree.

2. All the irritants investigated (scratch, pinch, burn, electrolysis, freezing, mosquito bite, dermographic scratch) tend to cause: (a) Initial pallor; (b) peripheral red zone; (c) reversion of color from pale to red, the latter commencing at the periphery and proceeding toward the center.

3. The tissues studied tend to react in one stereotyped manner to all the irritants investigated.

REFERENCES

1. Jankowsky, Gustav: Inaugural Dissertation, Breslau, 1887.

2. Lapinsky: Ueber den Mechanismus uns die Diagnostiche Bedeutung der Dermographie am oberen Theile des Rueckens und am hinteren Theile des Halses, Zeitschrift für die Gesamt. Neurologie und Psychiatrie, 22, 1914.

3. Chambard (quoted by Lapinsky): Dermographie observee sur un alcoolique, Archiv. de Neurologie, 1884.

THE DETERMINATION OF VENTRICULAR PREDOMINANCE FROM THE ELECTROCARDIOGRAM

HAROLD E. B. PARDEE, M.D.
NEW YORK

Two recent articles containing much speculation and few facts have directed my attention to the necessity for a review of the subject of the electrocardiographic diagnosis of hypertrophy of one or the other ventricle of the heart. The original observations on this subject were that cases in which hypertrophy of the left ventricle might be expected showed a relatively tall R wave in Lead 1, with absence of an S wave in this lead, while Lead 3 shows a relatively small or absent R wave and a deep S wave. In like manner, cases in which hypertrophy of the right ventricle might be expected showed a relatively small R wave in Lead 1 and a deep S, while the S wave was absent in Lead 3 and the R wave relatively tall.[1] Einthoven demonstrated the fact that if the actual values of the largest waves of the Q R S group in Leads 1 and 3 were added together, the result would be equal to the value of the largest wave of this group in Lead 2. There is some slight error in this addition owing to the fact that the peaks of the waves do not occur at the same instant of the heart cycle in all three leads. He showed that throughout the Q R S group and in fact throughout the whole electrocardiogram if we consider the parts of the curve in the three leads which occur at the same instant of time then the value in Lead 1 + value in Lead 3 = value in Lead 2.[2] From the relative size and direction of these values in the three leads there can be calculated the direction of flow of current within the heart at that instant.

It soon developed that it was not the actual hypertrophy of one or the other ventricle which caused the changes in the electrocardiogram, but the relation of the state of hypertrophy of each ventricle to the other. If a heart had mitral stenosis and had also to oppose an increased blood pressure, then both ventricles would become hypertrophied and the electrocardiogram might show a normal relation of the height of the R waves in the three leads. Neither ventricle in this case would be predominantly hypertrophied, and for this reason it has become necessary to speak of the records as showing right or left ventricular predominance instead of hypertrophy.

---

1. Einthoven, W.: Le Telecardiogramme, Arch. Internat. de Physiol. **4**:132, 1906.

2. Einthoven, W.: Weiteres u. d. Elektrokardiogram, Arch. f. d. ges. Physiol. **122**:576, 1908.

Various methods have been suggested for deriving from the electrocardiogram a mathematical expression of this relative predominance of one or the other ventricle. Einthoven considered that the current at the instant of the highest peak of the Q R S group would give such an index, and calculated from the size and direction of these peaks in the three leads the direction of the current within the heart which had caused these high peaks. This calculation was made by quite sound mathematics, and a table was published by him,[3] by the use of which it was very easy to determine the direction of the current within the heart which had produced corresponding waves in the three leads. This is simple enough when the peaks of the waves occur at the same instant of the heart cycle in all three leads, for then the formula Lead 1 + Lead 3 = Lead 2 will be exactly fulfilled. When they do not occur at the same instant they are spoken of as being "out of phase," but even in such records it is usually possible to determine by inspection which parts of the Q R S groups of the other two leads correspond in time with the high peak of the lead showing the largest deflection. This is aided by bearing in mind that in right predominance it is usual to have the peaks of the R waves in Leads 2 and 3 practically simultaneous while the corresponding instant in Lead 1 will lie somewhere on the downward stroke between the peaks of R and S. Likewise, in left predominance records the peaks of R are practically in phase in Leads 1 and 2, and this instant will fall in Lead 3 at a point on the downward stroke between the R and S peaks. Rarely, however, a record will defy even this attempt at analysis.

Having determined the direction of the current which produced the largest deflection, Einthoven considered that those hearts which showed this angle within the sector between 40 and 90 degrees below a line drawn horizontally to the patient's left were hearts which showed a normal balance of the ventricular elements. Those which gave an angle above 40 degrees showed left predominance, while those which gave an angle which was to the patient's right of 90 degrees showed right predominance. This was in general agreement with the previous idea as to the relation of the R and S waves in Leads 1 and 3 to ventricular predominance, for the S waves become more prominent than the R, in Lead 1 at 30 degrees and in Lead 3 at 90 degrees.

Lewis suggested a method of obtaining an index of predominance by adding the value of R1 — R3 to the value of S3 — S1.[4] He probably did this, although he did not attempt a theoretical explanation of this formula, from a belief that as R1 and S3 vary together, the first grow-

3. Einthoven, Fahr and de Waart: Ueber die Richtung und die Manifeste Groesse der Potentialsehwankungen, etc., Arch. f. d. ges. Physiol. **150**:275, 1913.

4. Lewis, T.: Observations on Ventricular Hypertrophy, etc., Heart **5**:367, 1914.

ing smaller and the latter larger with increasing left predominance they must governed by the left ventricle, and for a similar reason S1 and R3 must be governed by the right ventricle.

White has suggested that (U1 + D3)—(D1 + U3) considering that U, the upper deflection and D, the largest of the downward deflections, whether it be a Q or an S, would represent opposing ventricles.[5] His figure will, of course, only differ from Lewis' figure when Q is larger than S, so that it becomes the largest downward deflection.

Carter has suggested that the sum of the downward deflections of each lead be subtracted from the upward, and that the resulting figures for the three leads be used to determine the direction of the current within the heart.[6] When the resulting figures for the three leads cannot be made to agree with Einthoven's rule of Lead 1 + Lead 3 = Lead 2, by a little judicious scaling of the figures, he then recommends that the Lead 1 and Lead 3 values be used to determine the direction of the current, totally disregarding Lead 2.

COMPARISON OF L/R WEIGHT RATIOS AND ELECTROCARDIOGRAPHIC PREDOMINANCE AS DETERMINED BY FOUR METHODS

Case	L/R Weight Ratio	Angle as Found by Einthoven's Method	Angle as Found by Carter's Method	Lewis' Formula	White's "Index"	Value Largest Wave of QRS Group	Lewis' Formula Reduced to R : 10
I	2.03*	—10	—20	29.5	29.5	16.5	17.9
II	2.00	—70	—60	19.0	19.0	15.0	12.6
III	2.55*	—74	—75	17.5	16.5	15.0	11.7
IV	2.04	14	16	19.0	19.0	12.5	15.2
V	1.97*	79	75	—10.0	—8.0	13.0	—7.7
VI	1.94	45	30	8.0	8.0	11.0	7.3
VII	1.87	0	10	12.5	12.5	10.0	12.5
VIII	1.82	18	35	4.5	4.5	6.0	7.5
IX	1.00	82	115	—7.0	—7.0	6.0	—11.6
X	1.55*	4	—30	9.0	9.0	7.0	12.9
XI	1.38	78	90	1.5	1.5	6.5	2.3
XII	1.30*	79	95	—3.5	—5.0	5.0	—7.0
XIII	0.82*	101	150	—6.0	—6.0	6.0	—5.8
XIV	0.82	105	128	—15.5	—15.5	11.0	—14.1
XV	0.41	131	160	—77.0	—76.0	44.0	—17.5

* The cases marked with asterisk are from Cotton's series, the remainder are from Lewis'.

A great deal could be said about the theoretical merits of these different methods of estimating ventricular predominance. It can all be discarded, however, in the face of direct evidence such as we are able to obtain from two series of observations. One series of nine cases by Lewis [4] and one of six cases by Cotton,[7] have been reported in which the electrocardiogram and the actual weights of the ventricles

5. White, P. D., and Bock, A. V.: Electrocardiographic Evidence of Abnormal Ventricular Preponderance, etc., Am. J. M. Sc. **156**:17, 1918.

6. Carter, E. P.: The Electrocardiogram and Ventricular Predominance, Arch. Int. Med. **24**:638 (Dec.) 1919; also Carter, Richter and Greene: Bull. Johns Hopkins Hosp. **30**:162, 1919.

7. Cotton, T.: Observations on Hypertrophy, Heart, **6**:217, 1917.

were obtained in the same patients. These fifteen cases have been arranged in the accompanying table according to the ratio of the ventricular weights as determined by Lewis and Cotton. From the published measurements of the Q R and S waves in the three leads, the electrocardiographic "predominance" has been calculated by the four methods which have been mentioned. The first column is the value of L/R obtained from the ventricular weights. The figures for the angle of the largest current as obtained by Einthoven's method are shown in the second column; the angle as obtained by Carter's method is in the third column; the figures by Lewis formula are in the fourth column, and White's "index" occupies the fifth column.

It is evident that all of these formulas give figures which follow in a general way the actual relation of the ventricular weights, but it is also evident that none of them enables us to place the heart very accurately in the scale of left or right predominance as actually determined by the weight relation. The normal variations of the L/R weight ratio have been determined in two series of thirty-four normal persons, whose ventricles were separated and weighed by Lewis [4] and by Cotton.[7] The average L/R ratio was approximately 1.80, the extreme variations being 2.17 and 1.47, the former probably representing a moderate left predominance and the latter a moderate right predominance. Three of the cases of the table have an L/R ratio larger than 2.17, and therefore may be considered to show definite left predominance, while five have a ratio less than 1.47 and show, therefore, a definite right predominance.

Figure 1 is a series of curves constructed from the table by using the values in the first five columns to obtain the height from the base line and the order of the cases from 1 to 15, as determined by their L/R weight ratio, to obtain the distance from the left hand ordinate. The weight ratio forms a smooth steadily declining curve, while all of the other curves, though in general declining, have many departures from smoothness. Individual cases vary considerably from the position in these irregular curves which they would be expected to occupy considering their L/R ratio. The dotted line drawn through each curve indicates the average course of this curve, and along this line our cases should lie. It is evident that the variations from this average obtained by the Lewis or the White formulas are less than the variations obtained by the other formulas, and, moreover, only three persons who had a normal weight ratio would be classed as having predominance by these methods while either of the other methods would have thus misplaced four cases.

In considering the basis of the Lewis and White formulas, it is evident that the size of the largest wave in the Q R S group, R or S,

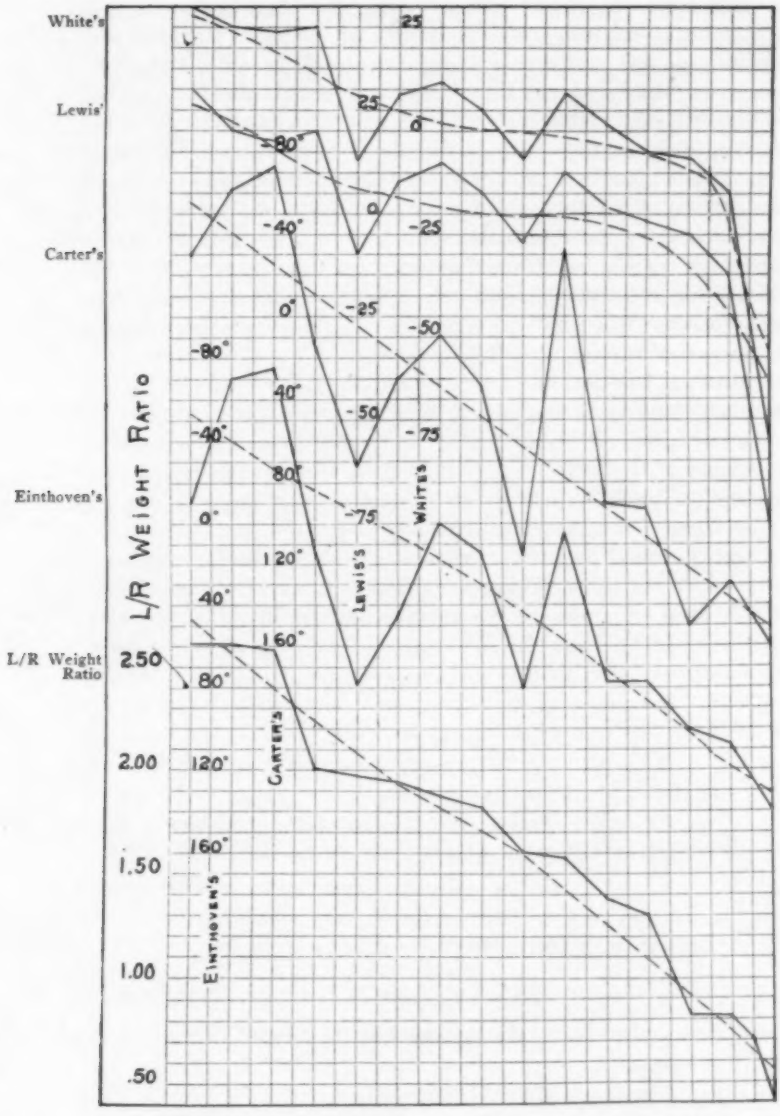


Fig. 1.—Series of curves constructed from the table by using the values in the first five columns to obtain the height from the base line.

as the case may be, will be an important factor in the resulting figure. The values for the largest waves in the electrocardiogram of each individual are shown in the sixth column of the table, and it is very interesting to note that they are larger in the right and left predominance cases than they are in those showing a normal balance. This is a wholly unexpected finding, and will well warrant a further study which is at present in progress. Considering this varying value of the largest waves, and the fact that the Lewis and White formulas as so evidently dependent on this value, it is not surprising that the curve of these cases obtained by these formulas show at first a steep descent as the diminishing degrees of left predominance are recorded, a more or less level stretch and then another steep descent as the increasing right predominance is met with. This fact made it seem advisable to correct the Lewis formula for the value of the largest wave in the record of the individual changing the Lewis figure, so that it would be proportional to a value of 10 mm. for the largest wave. This formula would be "Lewis' figure : X = R : 10." The figures obtained thus form the last column of the table. The variations in a curve constructed from these figures would be very great, so that this correction for the size of the largest wave offers no advantage.

Other formulas were tried attempting always to find a method of treatment of the electrocardiogram of these cases which would place the individual case near to the average position in the series which might be expected from the L/R ratio. They were all unsuccessful, none being any better than Lewis' formula which has such a desirable simplicity. The following were tried, but it seems unnecessary to publish the figures in view of their negative value.

1. $Q_1 + R_1 + S_3 - Q_3 - R_3 - S_1$, a formula suggested by Lewis' recent analysis of the electrocardiogram.[8]

2. $Q_1 + S_3 - Q_3 - S_1$ was tried because the R wave has probably a factor from both ventricles, while Q and S have not.[8]

3. $R_1 + S_3 - S_1 - R_3 +$ value of largest wave: another attempt to correct for the varying value of the R wave which has been noted with predominance of either ventricle.

4. $\frac{Q_1 + R_1 + S_3}{Q_3 + R_3 + S_1}$ an attempt to obtain an L/R ratio from the waves of the electrocardiogram which, according to Lewis,[8] depend on the respective ventricles.

5. The figure obtained by this last method was divided by the value of the largest wave.

---

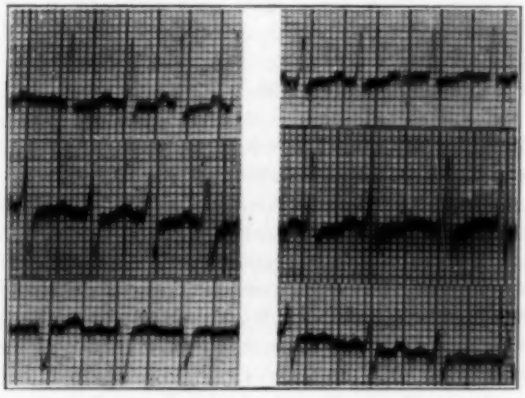
8. Lewis, T.: The Spread of the Excitatory Process in the Vertebrate Heart, Phil. Tr. Roy. Soc. London **207**:221, Series B, 1916.

DISCUSSION

As has been said, none of these methods attained the desired result of a uniformly varying series of figures, such as is given by the L/R weight ratio.

Let us consider possible reasons why this object could not be achieved. (1) It cannot be considered that the Q R S group is not governed by the ventricular weight ratio for *all* of the formulas derived from the records give figures which agree in a general way in their placing of these cases in the series of predominance. (2) It is possible that the cutting and weighing of the hearts might have been inaccurate so that the L/R ratio obtained does not express the proper position of the heart in the predominant scale. This cannot be considered, for it would not cause more than relatively slight variations in the L/R ratio for relatively large errors in cutting, and so would not account for more than a very slight displacement of the heart from the position in the scale of predominance. (3) There may have been errors in taking the electrocardiogram, but this cannot be considered at all likely in the hands of technicians who are familiar with the instrument as these men were. (4) It is possible that the individual hearts varied in some other way than in their ventricular mass so as to change the electrocardiographic record from what it would otherwise have been, thus displacing it in the scale of predominance. (a) The possibility that any of the cases of this series were suffering from blocking of one bundle branch may be discarded, for both of the workers are thoroughly familiar with the effect of this lesion on the record, and with the lack of relation between such curves as it would produce and the problem of ventricuular predominance which they were investigating. They would have discarded such cases. (b) The anatomical position of the heart within the chest might vary sufficiently to be responsible for these electrocardiographic variations. The respiratory movements of the diaphragm may cause a variation of as much as 30 degrees in the electrical axis of the heart,[3] and as it is a matter of common knowledge that in some types of individuals the heart may be more or less transversely placed on a high diaphragm as with full expiration, or in others may be more or less vertically placed with a low diaphragm as in full inspiration. The transverse type of heart, if otherwise normal, gives an electrocardiogram approaching the left predominance type, while that of the vertical heart approaches the right predominance type, and it is suggested that it is probably such differences in position as this which are responsible for the electrocardiographic variations which have caused the normal cases of this series to appear to have a ventricular predominance. By a similar mechanism a heart with a slight left predominance might give an electrocardiogram within the normal

limits of variation if it were vertically placed, or a slight right predominance might give a normal record if the heart were horizontal. The same mechanism would give to the electrocardiogram a form characteristic of a greater degree of predominance than the heart muscle actually shows if the left predominance case should lie transversely and the right predominance vertically. (c) Still another possibility has been sugugested,[9] for the discrepancies existing between the ventricular weight ratio and the electrocardiographic "predominance." The size of the ventricular cavity may vary for the same weight of muscle. This may be expressed as dilatation. A small thick-walled ventricle may weigh the same as a large thin-walled ventricle. The different distribution of the electrical potential which this would cause



A B

Fig. 2.—Two electrocardiograms taken from the same person; A, in the relaxed sitting position; B, in the erect sitting position.

would in all probability have its effect on the electrocardiogram, and might well lead to such variations as were observed in this series. This point of view has been elaborately discussed quite recently by Fahr,[10] and certainly should command attention from anyone who considers this problem. It is a most difficult hypothesis to investigate, however, as it necessitates careful measurement of ventricular diameters as well as of ventricular weight.

Either of these latter suppositions would explain why the electrocardiograms of this series which vary from their expected position in the predominance scale, vary in the same direction, i. e., toward right or

9. Personal communication from Dr. Hubert V. Mann.

10. Fahr, G.: An Analysis of the Spread of the Excitation Wave, etc., Arch. Int. Med. **25**:146 (Feb.) 1920.

toward left predominance, by whatever method the electrocardiogram is analyzed. The electrocardiogram has been caused to vary from the form which it would derive from the ventricular weight ratio by an unusually transverse or vertical position of the heart, or by what virtually amounts to a deformity of the heart, a dilatation of one chamber. It is impossible to decide between these hypotheses on theoretical grounds, but I must say that the former appears to be the more attractive theory.

Figure 2 shows two electrocardiograms taken one after the other from the same individual. Both were taken while he was sitting upright in a chair, but the one to the left, A, was taken with the erector spinae relaxed, the back bowed forward and the thorax fallen downward upon the abdomen so that the diaphragm was pushed up within it: the typical relaxed sitting position. The other record, B, was taken while he was sitting with the back straight and the chest forward in a normal, erect, sitting position. The electrical axis of record A is 6 degrees, while that of B is 46 degrees, the change by the Lewis formula is from 12 to 7, a change in this case due entirely to a change in the position of the diaphragm from high to normal. This patient was examined with the fluoroscope, and the anatomic axis of the ventricles roughly estimated in each position. This axis was found to rotate about 30 degrees. The degree of variation in the electrocardiogram which may result from a different position of the diaphragm is evident from this experiment, and also the fact that the anatomic axis varies at the same time in a similar manner.

CONCLUSIONS

The conclusions which may be drawn from these considerations are:

1. That the form of the Q R S group of the electrocardiogram is dependent in otherwise normal hearts on the relative weights of the two ventricles. An increase in the L/R ratio, such as would result from the left ventricle becoming relatively heavier, is accompanied by characteristic changes in the electrocardiogram, while if the L/R ratio is decreased, as by the right ventricle becoming relatively heavier, there are other equally characteristic changes in the record. These changes are the ones which have always been associated with the predominances; a tendency for R_3 to be relatively small, and R_1 and S_3 to be relatively large in left predominance, while R_1 is small and S_1 and R_3 are relatively large in right predominance.

2. Attempts to devise a formula from the Q R S waves by which the heart can be placed properly in a series of ventricular predominance are successful only in a general way. Individual electrocardio-

grams vary greatly from the position in the scale of ventricular predominance which the ventricular weights alone would lead us to expect them to occupy.

3. Of all the formulas which have been considered for determining the ventricular predominance from the electrocardiogram, the simplest to apply, the one giving the smallest apparent error in this series of fifteen cases, and the fewest variations of individual hearts from the position in the predominance scale which would be expected from the L/R weight ratio, is the formula suggested by Lewis of (R1 + S3)—(S1 + R3).

4. It is suggested that the cause of these variations may well be that the hearts which varied from their expected position in the scale of predominance were of the markedly transverse or vertical type so that the electrocardiogram was distorted by this position of the heart.

5. The suggestion as to ventricular dilatation causing these variations is also worthy of consideration.

The diagnosis of ventricular predominance is far from being the most important information which the electrocardiogram gives us, but it is nevertheless very suggestive and important in certain cases. It is well, therefore, that we should realize that our conclusions as to predominance are not always in agreement with the ventricular weights, and that we earnestly try to find what are the factors which interfere with this agreement. The present suggestion as to the cause of the inexactness of the electrocardiogram seems to me to be quite reasonable, but reasonableness alone, without an experimental basis, should never be the foundation of any medical diagnostic procedure. It is hoped that this discussion will stimulate many observers to note the anatomic position of the heart in relation to the electrocardiographic "predominance" which is shown, and that as many as possible will combine with these factors the necropsy data, consisting of the actual relation of the ventricular weights, using Lewis' technic for cutting and weighing the ventricles [4] so that the results may be comparable with his, and also proper measurements of the ventricular size. Only in this way can the subject be eventually placed on a firm foundation.

THE EFFECT OF ACUTE YELLOW ATROPHY ON METABOLISM AND ON THE COMPOSITION OF THE LIVER*

WILLIAM C. STADIE AND DONALD D. VAN SLYKE
NEW YORK

In the present paper we report chemical analyses of the blood and urine made in a case of acute yellow atrophy for three days before death, together with analysis of the liver removed at necropsy three hours after death. The study was directed especially toward the nitrogen metabolism and the acid-base balance of the patient. Besides other determinations, including those of urea, quantitative estimations of the amino-acid nitrogen in the urine, blood and liver were performed for the first time in such a case, so far as we can ascertain.

The results are of interest in two connections: (1) the pathologic metabolism of acute yellow atrophy, and (2) the rôle of the liver in the normal handling of nitrogenous products. The condition is one in which the liver as a functioning organ suffers almost complete, if not complete, destruction, without similar apparent injury to other organs; and the failure in yellow atrophy of definite steps in nitrogenous metabolism may be taken as an indication of the possibility that such steps are normally achieved either by the liver or with its aid.

REVIEW OF LITERATURE

Since Frerichs[1] (1861) established the presence of leucin and tyrosin in both the liver and urine in acute yellow atrophy, there has been basis for the belief that in this disease the liver proteins are digested to amino-acids, which are excreted as such in the urine. Schultzen and Reiss[2] (1869) are quoted as declaring that the presence of leucin and tyrosin in the urine indicates acute yellow atrophy as definitely as the presence of albumin indicates nephritis. In nearly all cases reported, however, the amino-acids have been identified only by microscopic examination of the crystals, and Röhmann[3] (1888) with the utmost care was unable definitely to identify either leucin or tyrosin in the antemortem urine in a case terminating fatally. Röhmann explained the failure of these substances to appear in some cases of yellow atrophy by the hypothesis that amino-acids are excreted only when formed at a rate faster than they can be destroyed in the body. In his case an aromatic acid, probably p-hydroxyphenyl lactic acid, formed by replacing the NH_2 group of tyrosin by an OH (Ellinger and Kotake,[4] 1910), was obtained from the urine. Its presence indicated that the body could still deaminize tyrosin, even though the product of deaminization failed of further combustion.

---

* From the Hospital of The Rockefeller Institute for Medical Research.

1. Frerichs: Klinik der Leberkrankheiten, Braunschweig, 1861.
2. Schultzen and Riess: Hammarsten's Lehrb. d. Physiol. Chem., Ed. 8, Wiesbaden, 1914, p. 705.
3. Röhmann: Berlin. klin. Wchnschr. 861, 882, 1888.
4. Ellinger and Kotake: J. Biol. Chem. **5**:129, 1908.

Neuberg[5] (1909) claimed to have obtained from the blood serum in a fatal case tyrosin, leucin and lysin, the three amino-acids together amounting to about 6 gm. per liter of blood. This indicated the presence of so great an amount of amino-acids in the blood, that the investigators believed they must be due to autolysis of the muscles as well as the liver. At the same time, the nitrogen distribution in the urine was normal, 76 per cent. of the total nitrogen being in the form of urea. The results of the blood and urine analyses are both so unusual and so completely at variance with each other (i. e., tremendous amounts of amino-acids in the blood with no apparent disturbance of the nitrogen distribution in the urine) that without confirmation their acceptance as accurate in a quantitative sense is difficult.

Wells[6] (1909) has published the most complete examination of the liver in yellow atrophy. He submitted the noncoagulable, water-soluble extract to Fischer's ester process for isolation of the mono amino-acids, and to Kossel's procedure for the diamino acids, and identified histidin, lysin, tyrosin, leucin, glycin, alanin, prolin, glutaminic acid and aspartic acid, the total amount being 8.67 gm. from the entire liver. To judge from the usual losses by the ester method, the amounts present were probably twice as great as those actually obtained. Wells proved beyond doubt that the liver in acute yellow atrophy does contain considerable amounts of the various amino-acids yielded by proteins on hydrolysis. That previously only leucin and tyrosin were, as a rule, found was obviously due to the fact that these are the amino-acids which are most easily obtained by crystallization.

Even the results of Wells, however, did not entirely solve the problem from a quantitative standpoint. Van Slyke and Meyer[7] (1912), and Abel, Rowntree and Turner[8] (1914) showed that amino-acids in considerable amounts are *normal* constituents of the blood and tissues. The conceptions of the changes in liver atrophy, and their significance in regard to liver function, therefore, became dependent on the question whether or not the amounts of amino acids formed and excreted in acute yellow atrophy vary significantly from the normal. In the present paper we are able to answer this question in the affirmative, and thereby confirm the older conceptions of the metabolism in this disease and, we believe, place them on a more complete experimental basis.

REPORT OF CASE

The patient, female, aged 29 years, had been well to within one day of admission to the hospital. Her first symptoms were nausea and vomiting, at first mild, but persistent and gradually increasing in intensity. She had no chills, fever or pain. There was slight headache. Bowels were slightly constipated. The vomitus consisted of greenish, bile-tinged fluid.

On admission to the hospital, physical examination showed temperature was 100, pulse 75, respirations 20. Sclerae showed a very slight but definite icterus. Heart and lungs were negative. Abdomen negative. Liver and spleen not felt. Skin negative; no jaundice.

Second day.—Patient continued vomiting all day; no pain. Temperature 99.6. Definite jaundice had developed over the entire body.

Third day.—Vomiting persistent and intractable. She was unable to retain even water by mouth. Jaundice much more marked.

Fourth day.—She was very weak and restless. No pain; no headache. All measures to allay the continuous vomiting were unsuccessful. Jaundice deeper. The abdomen, heart and lungs continued negative. Pulse 90, respirations 20, temperature 100.0 F.

---

5. Neuberg and Richter: Deutsch. med. Wchnschr. **30**:499, 1904.
6. Wells: Arch. Int. Med. **9**:628, 1907.
7. Van Slyke and Meyer: J. Biol. Chem. **16**:197, 1913.
8. Abel, Rowntree and Turner: J. Pharmacol. Exper. Therap. **5**:275, 1914.

Fifth day.—Patient vomited continually. Later she gradually sank into coma. No convulsions. Sclerae and skin of a deep greenish-yellow color. Pupils were widely dilated but equal, and reacted slightly to light. Fundi oculi showed nothing. Blood pressure, 155/70. Abdomen soft. Liver and spleen not felt. Liver dulness extended from fourth rib to just below the costal margin. All extremities quite rigid, no Kernig. Exaggerated knee jerks on both sides. Marked double ankle clonus. Definite Babinski on the left side, none on the right. No Chvostek or main d'accoucheur.

Lumbar puncture: No increased pressure. Fluid clear, cells 5 per c.c.; spinal fluid urea nitrogen, 0.073 gm. per liter. No bile (Smith's test).

In the late afternoon rigidity of the extremities and Babinski disappeared, and the knee jerks became less marked. No convulsions at any time or further evidence of tetany. No subcutaneous hemorrhages; at point of pressure, however, by the bed clothes there were small areas of ecchymosis. No diminution of the liver dulness made out during the day.

Sixth day.—Patient continued comatose, temperature and pulse rapidly rising. At 8 a. m., temperature was 108; pulse, 145; respirations, 44. No decrease of liver dulness made out.

Patient died at 8:33 a. m.

Wassermann completely anticomplementary.

Necropsy findings.—Macroscopic: Skin was deeply jaundiced, of a yellowish green color. Lungs were normal, except for a few scattered, hemorrhagic patches. Heart was negative. Abdomen: Omentum and the mesentery showed everywhere numerous hemorrhagic areas from 3 to 5 cm. in diameter. Stomach and intestines, gallbladder, pancreas, kidneys, suprarenals and uterus were normal. Ovaries contained few cysts. Spleen not enlarged; extremely dark in color. On section it was quite soft. Cut surface was a very dark purplish red. Malpighian bodies were not well made out.

Liver was quite markedly diminished in size. It was not found fallen away from the anterior abdominal wall. Its upper border corresponded with the fourth rib; its lower border to the costal margin. Weight, 1,000 gm. Capsule was smooth, and the parenchyma shining through appeared quite yellowish. Liver substance was extremely friable and cut with great ease. On section, the liver surface showed at the center of each lobule a dark reddish area surrounded by a lighter yellow zone. This appearance was quite uniform throughout the entire liver, except that there were occasional patches from 5 to 10 mm. in diameter of a darker red, and these areas were sunken below the general surface. Other areas, larger in size, were yellowish and studded with small reddish points representing the centers of the lobules. In these yellowish patches the centers of the lobules were smaller and less numerous than in other parts of the liver. There were no areas which suggested adenomatous hyperplasia.

Microscopic: Only the liver and kidney appeared abnormal under the microscope. The uterus, spleen, suprarenals, pancreas, lungs and bladder were examined, with negative results.

Kidney: There are scattered throughout the cortex small areas of hemorrhage between the tubules and in Bowman's capsule. Glomeruli appear quite normal, but the tubules show here and there a moderate degree of fatty infiltration and cloudy swelling. Otherwise the parenchyma was normal.

Liver: Universally, the histologic picture is characterized by an extensive destruction. Throughout most of the liver, cells are represented by only faint outlines with completely or partially disintegrated nuclei. In some areas the liver cells are represented only by a structureless debris, while in others the outlines of the cell bodies can be faintly made out still in lobular arrangement. There is an extensive fatty infiltration. These changes involve practically all of the lobule ,but are most extensive at the periphery. At the center of each lobule the bile duct epithelium is practically intact, and here may be found quite generally very few liver cells in a better state of preservation. Some of the

bile ducts are surrounded by well preserved liver cells arranged in strands. Scattered throughout, mainly at the periphery of the lobules, are areas of blood extravasation.

Analyical Methods.—Urine Analyses: Chlorids were titrated by the Volhard method. Urea was determined by Van Slyke and Cullen's[9] (1917) modification of Marshall's urease method, using Squibb's urease prepared from Jack beans, ammonia by the aeration technic described by Van Slyke and Cullen. The total amino-acid nitrogen was determined as described by Levene and Van Slyke[10] (1912), the creatinin by Folin's[11] (1905) method, and the uric acid by Folin and Shaffer's[12] (1901) method. Total acetone bodies were estimated by Van Slyke's[13] (1917) gravimetric method. The titratable acid was determined according to Folin[14] (1903) by titration with phenolphthalein in the presence of potassium oxalate.

Blood Analyses: The urea was determined as described by Van Slyke and Cullen[15] (1914), the amino-acid nitrogen by Van Slyke's nitrous acid method as described by Whipple and Van Slyke[16] (1918). The plasma bicarbonate was estimated by the carbon dioxid capacity method of Van Slyke and Cullen[9] (1917).

Liver Analysis.—Water content: Three samples of from 2 to 3 gm. weight each from different lobes of the liver were dried in glass dishes at 110 C. to constant weight. The results were 71.6, 71.6 and 71.9 per cent. water.

Total Nitrogen.—The dried samples used for water determination were Kjeldahlled. The results were 8.0, 8.36 and 9.0 per cent. of nitrogen calculated on the dried samples, and 2.28, 2,34 and 2.51 per cent. calculated on the fresh samples, an average of 2.38 per cent. of the fresh substance, or 8.45 per cent. of the dried. Using the approximate factor 6.25 for conversion of nitrogen figure into protein figure, this would indicate that 5.3 per cent. of the dry substance was protein.

Fat.—Three samples of from 6 to 12 gm. from different lobes were let stand over night with 100 c.c. of 95 per cent. alcohol each. The alcohol was poured off, the liver samples were minced, and were extracted with ether in a Soxhlet apparatus. The alcohol extracts were concentrated nearly to dryness, taken up with ether, and combined with the ether extracts. The latter were concentrated to dryness, and taken up with petroleum ether in weighed flasks. After the petroleum ether had been mostly removed on the water bath, the flasks were dried in an evacuated desiccator over sulfuric acid to constant weight. The results were 12.7, 13.8 and 14.0 per cent. of fat, an average of 13.5 per cent. of the fresh liver, or 47.7 per cent. of the dry substance.

Extraction of Nonprotein Nitrogen.—Three samples, totalling 303 gm., were cut with scissors into pieces which were dropped into 1.5 liters of boiling water slightly acidified with acetic acid. After the tissues were coagulated, the water was decanted, the pieces were minced, and the extraction with hot water was repeated three times. The decanted extracts were filtered through glass wool, then mixed with 50 gm. kaolin, and filtered through paper with suction, the residue being washed with hot water. The clear amber filtrate was boiled down in an enamelled ware vessel to about 500 c.c., and poured into three volumes of absolute alcohol to complete the removal of proteins. The next day the pre-

9. Van Slyke and Cullen: J. Biol. Chem. **30**:289, 1917. Van Slyke, Stillman and Cullen: J. Biol. Chem. **30**:401, 405, 1917.
10. Levene and Van Slyke: J. Biol. Chem. **12**:301, 1912; **16**:125, 1913.
11. Folin: Am. J. Physiol. **13**:48, 1905.
12. Folin and Shaffer: Ztschr. physiol. Chem. **32**:552, 1901.
13. Van Slyke: J. Biol. Chem. **32**:455, 495, 499, 1917.
14. Folin: Am. J. Physiol. **9**:265, 1903.
15. Van Slyke and Cullen: J. Biol. Chem. **19**:211, 1914.
16. Whipple and Van Slyke: J. Exper. M. **28**:213, 1918.

cipitate which formed was filtered off, and washed with 80 per cent. alcohol. The filtrate was concentrated under reduced pressure and brought to a volume of 150 c.c.

Free Amino Nitrogen.—Two c.c. portions of extract were used for the determination of amino nitrogen by the nitrous acid method of Van Slyke[17] (1912), the reaction being continued for 3.5 minutes at 22 C. The volume of gas yielded in three determinations was 9.55, 9.50 and 9.65 c.c. at 22 C., 761 mm., the average, 9.57 c.c., indicating 5.40 mg. of amino nitrogen, or 134 mg. per 100 gm. of fresh liver.

Peptid Nitrogen.—Five c.c. samples of the extract were mixed in test tubes with 5 c.c. portions of concentrated hydrochloric acid and heated for twenty-four hours at 100 C. The hydrochloric acid driven off on the water bath, and the residue diluted to 20 c.c., of which 2 c.c. portions were used for the amino nitrogen determination. The determinations yielded 3.72, 3.67 and 3.63, average 3.67 c.c. of nitrogen at 22 C., 759 mm., indicating 206 mg. of amino nitrogen per 100 gm. of fresh tissue. Subtracting the 134 mg. present as per amino nitrogen before hydrolysis, leaves 72 mg. as peptid nitrogen, freed by hydrolysis.

Urea and Ammonia Nitrogen.—These determinations were made as in urine (Van Slyke and Cullen,[9] 1914), 5 c.c. of extract being used for urea and the same amount for ammonia. The results of triplicate determinations indicated 14.8 mg. of urea nitrogen and 34.5 mg. of ammonia nitrogen per 100 gm. of fresh tissue.

Creatinin.—Folin's method was used as for urine[13] (1905), except that the final dilution was less. Five c.c. of the extract were mixed with 15 c.c. of saturated picric acid solution, and 5 c.c. of 10 per cent. sodium hydroxid. At the end of five minutes the solution was diluted to 50 c.c. and read against a dichromate standard. The result, which may be somewhat high because of the relative concentration of sodium picrate, indicated 3.3 mg. of creatinin nitrogen per 100 gm. of fresh tissue.

Creatin Plus Creatinin.—Five c.c. of extract were heated at 100 C. with 5 c.c. of N hydrochloric acid for three hours. The hydrochloric acid was neutralized with concentrated sodium hydroxid, and 5 c.c. of 10 per cent. sodium hydroxid in excess were added with 15 c.c. of saturated picric acid. After five minutes the solution was diluted to 100 c.c. and read against a chromate standard. The reading indicated 17.6 mg. of creatin plus creatinin nitrogen, or 14.3 mg. of creatin nitrogen per 100 gm. of fresh liver tissue.

The technic used is similar to that employed by Janney and Blatherwick[18] (1915). The difference is that the above authors used aluminum hydroxid to adsorb uncoagulated protein (presumably gelatin), while we used kaolin. Creatinin under proper conditions is adsorbed by kaolin (Greenwald,[19] 1918), but we found by control tests that the kaolin preparation used by us in the amounts employed did not remove sufficient creatinin to significantly affect results such as were obtained.

DISCUSSION OF RESULTS

Excretion.—The comatose condition of the patient made collection of complete twenty-four hour specimens impossible, so that conclusions have to be drawn largely on the nitrogen distribution. The abnormalities in the latter during the last two days before death are the

17. Van Slyke: J. Biol. Chem., 1912.
18. Janney and Blatherwick: J. Biol. Chem. **21**:567, 1915.
19. Greenwald: J. Biol. Chem. **34**:103, 1918.

high ammonia ratio, and even more strikingly, the high amino acid nitrogen and the low proportion of urea nitrogen (Table 1). All three are explainable on the assumption that the liver had lost a part of its ability to transform amino-acid nitrogen into urea nitrogen, one portion being excreted in the form of unchanged amino-acids, and another in the form of ammonia.

TABLE 1.—SALT AND NITROGEN EXCRETION

Date, 1919	Output, C.c.†	Specific Gravity	Bile	NaCl, Gm. per L.	Total N, Gm. per L.	Urea N		Amino-Acid N		NH_3 N		Creatinin N		Uric Acid N		Undetermined N	
						Gm. per L.	Per Cent. of Total N	Gm. per L.	Per Cent. of Total N	Gm. per L.	Per Cent. of Total N	Gm. per L.	Per Cent. of Total N	Gm. per L.	Per Cent. of Total N	Gm. per L. Per Cent. of	Total N
Feb. 28	1,070	1.013	+	....	.....	3.11	....	....	....	0.392							
Mar. 1	250+	1.022	+	1.04	12.90	7.04	47.2	0.61	4.1	0.802	16.2	0.65	4.4	0.185	1.2	4.65	32.7
Mar. 2	411+	1.032	+	0.28	10.94	5.68	51.9	1.75	16.0	1.880	17.2	0.54	2.0	0.128	1.7	0.96	8.1
Mar. 3	130+	1.061	+	1.38	16.64	7.75	46.6	2.22	13.3	1.925	11.6	0.49	2.9	0.417	2.5	3.82	23.0

* Tyrosin crystals were obtained from the combined specimens of urine not used for other analyses.
† Part of urine was lost on March 1, 2 and 3 because of patient's comatose condition.

The amount of nitrogen eliminated cannot be stated accurately because of the lack of twenty-four hour samples of urine. The probable minimum can, however, be approximately estimated from the creatinin. The creatinin nitrogen excretion of an individual of the patient's size (about 50 kg.) would normally be about 4.40 gm. The twenty-four hour excretions of nitrogen and of ammonia plus titratable acid, estimated in this manner, are given in Table 2. In an acute illness

TABLE 2.—APPROXIMATE TWENTY-FOUR HOUR NITROGEN AND ACID EXCRETIONS ESTIMATED FROM CREATININ OUTPUT

Date	A	B Proportion of 24-Hr. Excretion in 1 Liter of Urine Sample Obtained, Estimated from Creatinin, $\frac{A}{400}$	Estimated Excretion per 24 Hours = Excretion per Liter Urine × B	
	Creatinin N per L. Mg.		Titratable Acid + NH_3, C.c. 0.1 N	Total N, Gm.
March 1	650	1.62	670	8.6
March 2	540	1.35	1,530	8.1
March 3	490	1.22	1,530	13.6

with pathologic tissue loss, the creatinin output might be increased. Even if it remained only normal at 0.40 gm. per day, however, the total nitrogen excretion on March 1, 2 and 3 would be calculated at 8.6, 8.1 and 13.6 gm., respectively, assuming that the ratio of twenty-four hour total nitrogen to the observed nitrogen per liter is as 0.40 to the observed creatinin nitrogen per liter. The first two figures

might be considered normal for a fasting individual (Lusk,[20] 1917) but the last is certainly high and corresponds with the incidence of fever.

Small amounts of acetone bodies were excreted, but in quantities not sufficient to be of significance for the acid-base balance of the body.

The low salt output was presumably due to lack of salt intake, rather than kidney retention.

TABLE 3.—Acid Excretion and Alkaline Reserve

Date, 1919	Excretion per Liter of Urine			Total Acetone Bodies, C.c. 0.1 N	Blood Plasma Bicarbonate CO_2, Volume per Cent.
	NH_3, C.c. 0.1 N	Titratable Acid, C.c. 0.1 N	Acid + NH_3, C.c. 0.1 N		
February 28	280	92.4	372		
March 1	616	460	1,076	64	
March 2	1,343	719	2,062	180	96.5
March 3	1,375	496	1,871	...	65.4
March 4	.....	...	.....	...	49.0

Blood Analyses.—The analyses of the blood, like those of the urine, indicate a loss of diaminizing function in the body (Table 4). The amino nitrogen contents on the last two days are respectively two and three times as great as the 7 to 8 mg. per 100 c.c. which represent the average normal (Bock,[21] 1917). The apparent explanation is that the liver had lost the ability to transform amino-acids into urea, an ability which has been demonstrated in the normal liver by the perfusion experiments of Salaskin[22] (1898) recently confirmed by Jansen (1915), and by the physiological experiments of Van Slyke, Meyer, Cullen and McLean (Van Slyke,[23] 1917).

TABLE 4.—Urea and Amino-Acid Nitrogen in the Blood

Date, 1919	Urea N, Gm. per L.	Amino-Acid N, Gm. per L.
February 28	—	—
March 1	—	—
March 2	0.123	0.140
March 3	0.088	0.173
March 4	0.159	0.263

The source of the amino-acids in the blood in our case was undoubtedly autolyzed tissue protein. The patient, because of the nausea, retained practically no food; the considerable amounts of nitrogen excreted (8 gm. or more per day) must have come from tissues autolyzed under the influence of the fasting and intoxication attending the disease.

20. Lusk: Science of Nutrition, Philadelphia, 1917.
21. Bock, J. C.: J. Biol. Chem. **29**:191, 1917.
22. Salaskin: Ztschr. f. physiol. Chem. **25**:128, 1898.
23. Van Slyke: Arch. Int. Med. **19**:56 (Jan.) 1917.

The blood urea remains within normal limits. Taken with the continued output of urea in the urine, it shows that the urea-forming function of the body, although diminished, was only partially lost, even on the day before death.

The blood plasma bicarbonate determinations (Table 3) gave a peculiar result on the first observation four days before death. The carbon dioxid capacity of 96.5 per cent. would indicate an abnormally high alkaline reserve. Unfortunately, the observation was not repeated on that day, and we are uncertain whether an increased blood bicarbonate actually existed, or whether there was an error in the determination. The carbon dioxid estimations were done in duplicate, but the carbon dioxid capacity might have been raised in vitro by contamination of the centrifuge tube or equilibrating funnel with alkali. That this may have occurred is made more probable by the fact that the excretion of titratable acid and ammonia on this day was above the usual normal limits.

On the last two days before death, there was a high exretion of titratable acid and ammonia, about double the normal, and on the day before death the plasma bicarbonate fell slightly below normal (49 per cent. of carbon dioxid). These facts indicate a definitely accelerated formation of acids in the organism, but neither the acid excretion nor the plasma bicarbonate indicates an acidosis sufficient to have in itself a definite effect on the patient's condition. (Compare Van Slyke,[24] 1917 [b]). In connection with the increased acid production it is of interest to note that Röhmann [8] (1888) obtained unusual aromatic acids and considerable amounts of sarcolactic acid from the urine in a case of yellow atrophy.

Composition of the Liver.—The most striking change in the liver was the marked loss of substance, which is usually noted in acute atrophy (Wells,[6] 1907). The liver weighed only 1,000 gm. instead of the 1,800 gm., which, for an individual of the patient's size, is normal, according to Frerichs [1] (1861).

The water content of 71.7 per cent. (Table 5) shows no increase over that of the normal liver analyzed by Wells, in fact is less than the latter (76.1 per cent.). In this respect this case differs from most of those in the literature, as the water content usually has been found high in acute yellow atrophy.

The fat content of 13.5 per cent. is decidedly high, the normal being quoted by Wells [6] (1907) as about 3 per cent. The livers of acute atrophy of which analyses are reported in the literature (Wells, 1907, 1908) have been found to vary between from 2.0 and 8.7 per cent. in fat content, while those of phosphorus poisoning and fatty degenera-

24. Van Slyke: J. Biol. Chem. **32**: (b) 455, 1917.

tion show from 25 to 30 per cent. In our case of acute atrophy the difference from the high fat values of phosphorus poisoning and fatty degeneration is much less striking than in any of the instances reported. It may be that the unusually rapid progress, with death a few days after the first symptom, prevented the complete combustion of the fat transported to or formed in the liver. The high fat content in our case is the cause of the normally high content of total solids noted in the preceding paragraph; fat increase makes up for the protein loss.

TABLE 5.—Dry Matter, Fat and Total Nitrogen in Liver

	Per Cent.		Normal Values, per Cent.*	
Water	71.7		77.6	76.1
Dry matter	28.3		19.4	20.9
Dry matter as fat	13.5	28.4	5.0	3.0
Dry matter as protein calculated as N × 6.25	14.9			

* From Wells (1908).

TABLE 6.—Nitrogen Distribution in Liver

A. Total N	Per 100 Grams Liver, Gm.	Proportion of Total N, per Cent.
Total N	2.380	100.0
Nonprotein N	0.315	13.2
Protein N (by difference)	2.065	86.8
B. Nonprotein N	**Per 100 Grams Fresh Liver, Gm.**	**Proportion of Total Nonprotein N, per Cent.**
Total nonprotein N	0.3139	100.0
Urea N	0.0148	4.76
Ammonia N	0.0345	10.95
Amino N	0.1340	42.50
Peptid bound N	0.0720	22.80 65.3
Creatin N	0.0143	4.54
Creatinin N	0.0033	1.05
Undetermined N	0.0421	13.40

The "dry matter not fat," which, as indicated by its nitrogen content, was nearly all protein, was much decreased, as it has been in all the reported cases of liver atrophy, whether due to poisoning or to acute disease. In our case the content of solids not fat, or approximately the protein, is 14.9 per cent. instead of the normal 20 per cent. of fresh liver. During the few days of the disease, the liver, therefore, in losing about 45 per cent. of its weight lost about 60 per cent. of the protein substance.

In the nitrogen distribution in the liver (Table 6) the main point of interest is the high content of amino-acid and peptid nitrogen. Compared with livers of normal dogs, the amino nitrogen, 0.134 per

cent. of the fresh tissue, is about three times as great (Van Slyke and Meyer,[7] 1913). The observed amino nitrogen content indicates the presence of approximately 13 or 14 gm. of free amino-acids in the 1,000 gm. of liver tissue.

RÔLE OF THE LIVER IN NITROGENOUS METABOLISM

The apparent significance of these figures, along with those for the blood and urine, is that the liver protein was autolyzed at a rapid rate to amino-acids and peptids, chiefly the former, and that amino-acids produced by the abnormal autolysis of the liver and the normal autolysis of the rest of the body (other organs were not macroscopically or microscopically degenerated) were turned into urea to the extent of only about 60 per cent. instead of from 85 to 95 per cent. The excreted amino-acids formed as high as 16 per cent. of the total urinary nitrogen instead of the normal 2 per cent.

There was no indication at any time of a tendency for the urea nitrogen output to fall much below 50 per cent. of the total nitrogen. In view of the apparently complete degeneration of the liver cells the data consequently suggest the probability that, although deamination and urea synthesis without the liver are incomplete, nevertheless they can occur to such an extent that the greater part of the nitrogen normally excreted as urea is still in this form. Fiske and Sumner[25] (1914) found that dogs could form urea from injected glycocoll even after the abdominal viscera had been excluded from the circulation. It is uncertain whether a considerable part of the total urea synthesis normally occurs in parts other than the liver, or whether the process is taken up elsewhere only when the liver fails.

It appears that acute yellow atrophy, with the possible exception of fatal phosphorus poisoning, is the only clinical condition in which unusual amounts of amino-acids have been demonstrated to be formed and excreted as such, without change to urea or ammonia.

The most rapid autolysis unaccompanied by liver degeneration does not apparently result in the excretion of amino-acids. For example, we have not found the amino nitrogen of the blood or urine increased during resolution in pneumonia, although this process represents one of the most striking examples known of rapid autolysis in vivo. Nor was any abnormal increase in the blood amino nitrogen observed by Whipple and Van Slyke[16] (1918) in dogs that were intoxicated by proteose or by intestinal obstruction in such a manner that the blood urea was raised by autolysis of body protein in a few hours to form two to five times the fasting level. Such urea changes indicate an amount of tissue digestion seldom met in disease, and not approximated in the apparently localized autolysis of yellow atrophy.

25. Fiske and Sumner: J. Biol. Chem. **18**:285, 1914.

In order that amino-acids in exceptional amounts shall escape deaminization and appear in abnormal amounts in the urine, it appears necessary not only that the liver shall be injured, but that its loss of function shall be profound, and, as stated above, such loss of function apparently has been observed in man with certainty only in acute atrophy. We have been unable to confirm the statement of Labbé and Bith [26] (1911) that it occurs in diabetes (Van Slyke and Stillman, unpublished results). It does not occur in the toxemias of pregnancy, despite the marked degenerative changes that occur in the liver (Losee and Van Slyke,[27] 1917). Levene and Van Slyke [10] (1912) failed to observe it in two cases of cirrhosis. Chesney, Marshall, and Rowntree [28] (1914) report somewhat increased amino-acid nitrogen in both blood and urine in more than 50 per cent. of a series of cases with apparent liver insufficiency from various causes. However, the upper limits for amino nitrogen which they assumed were so low (1.5 per cent. of the urine nitrogen, and 3 mg. per 100 c.c. of blood) that they are readily exceeded in normal individuals (Levene and Van Slyke,[10] 1912, 1913; Bock,[21] 1917; Cullen, Ellis and Van Slyke,[29] 1915). The only case in their series with definitely high blood amino nitrogen was one of arsphenamin poisoning, with 12.4 mg. per 100 c.c.

In pathologic liver conditions caused experimentally, it appears to be likewise unusual, unless liver degeneration is almost complete, to find increased amino acid content in blood or urine. Whipple and Van Slyke [16] (1918) failed to observe it in the blood of dogs with Eck fistulas (unpublished results). Levene and Van Slyke [10] (1912) did not find it in the urines of dogs in which Opie and Dochez had caused liver degeneration by phosphorus and chloroform poisoning. Only Marshall and Rowntree [30] (1915) observed an increase in the blood amino nitrogen (up to 21 mg. per 100 c.c.) shortly before death in dogs poisoned with phosphorus.

In pathologic conditions not involving the liver, Bock [21] (1917) found very markedly increased blood amino nitrogen only in some cases of nephritis, in which amino acids are retained along with other urinary constituents.

SUMMARY

An increased excretion of ammonia and titratable acids was observed in the last days of illness, and a fall of plasma bicarbonate to slightly below normal on the day before death. Even at this time, however, the deviations from the normal were too small to indicate that acid intoxication was a significant factor in the condition.

26. Labbé and Bith: Progrés méd. **27**:581, 1911.
27. Losee and Van Slyke: Am. J. Med. Sc. **153**:94, 1917.
28. Chesney, Marshall and Rowntree: J. A. M. A. **63**:1533, 1914.
29. Cullen, Ellis and Van Slyke: J. A. M. A. **64**:126, 1915.
30. Marshall and Rowntree: J. Exper. M. **22**:333, 1915.

The results afford confirmation of a quantitative character for the belief that amino-acids are formed by autolysis in the atrophying liver, and circulate and are excreted as such in unusual amounts.

The excretion of amino-acids did not appear to be due to increase in their rate of formation, for the total protein katabolism was not abnormally or even unusually rapid. The excretion appeared due rather to loss of power to deaminize amino-acids at even an ordinary rate.

A review of the known instances of rapid intra vitam autolyses not involving the liver indicates that tissue waste alone does not cause increase of amino acids in the blood and urine. In conditions of less profound liver injury (eclampsia) a marked decrease may occur in the proportion of urinary nitrogen present as urea and ammonia, which are partly replaced by as yet unidentified nitrogenous substances (undetermined nitrogen); but excretion of definitely abnormal amounts of amino acids appears to result only when the destruction of the liver cells is almost complete.

These observations support the view that in the deamination of amino acids and the synthesis of urea the liver bears a part which cannot be entirely assumed by the rest of the body.

INDEX TO VOLUME 25

PAGE

Allen, F. M.: Case of hereditary diabetes 648

Arkin, A.: Rat bite fever 94

Arthritis, studies on arthritis in army based on 400 cases; observations on basal metabolism; R. Pemberton and E. H. Tompkins 241

Arthritis, studies on arthritis in army based on 400 cases; preamble and statistical analysis; R. Pemberton and J. W. Robertson 331

Arthritis, studies on arthritis in army based on 400 cases; roentgen-ray evidences, clinical considerations, treatment, summary, conclusions and clinical abstracts of cases studied; R. Pemberton 351

Arthritis, studies on arthritis in army based on 400 cases; studies on nitrogen, urea, carbon dioxid combining power, calcium, total fat and cholesterol of fasting blood, renal function, blood sugar and tolerance; R. Pemberton and G. L. Foster 243

Auricular pacemaker, clinical observations on unusual mechanisms of; P. D. White 420

Bailey, C. V.: Toxic jaundice in patients under antisyphilitic treatment; study of chemical analyses of blood and urine, and observations on effect of exercise and diet in treatment of syphilis 628

Baumgartner, E. A.: Purulent typhoid meningitis 537

Bibb, L. B.: Sequence and arrangement of pallor and redness in irritated skin of normal and dermographic individuals 680

Blood platelet count and bleeding time in diseases of blood; H. C. Gram ... 325

Blood, protein and lipin content of blood serum in nephritides; M. Kahn ... 112

Blood sugar in depancreatized dogs; B. J. Delatour 405

Book Reviews: Neoplastic Diseases; J. Ewing 229
Pulmonary Tuberculosis 449
Syphilis and Public Health; E. B. Vedder 229
Total Dietary Regulation in Treatment of Diabetes; F. M. Allen, E. Stillman and R. Fitz 333

Breathing, harmful effects of shallow breathing with special reference to pneumonia; J. Meakins 1

Bronchitis, fetid spirillar bronchitis and pulmonary gangrene; P. Nolf 429

Buckman, T. E.: Studies on arthritis in army based on 400 cases; studies in relation of creatin metabolism to arthritis 335

Cancer, effect of roentgen rays on metabolism of cancer patients; R. N. DeNiord, B. F. Schreiner and H. H. DeNiord 32

Cerebrospinal fluid in multiple sclerosis; J. E. Moore 58

PAGE

Cerebrospinal fluid, study of colloidal gold reaction and its clinical interpretation; M. Warwick and C. E. Nixon..... 119

Chloroform poisoning, sodium carbonate in; E. A. Graham..... 575

Cholesterinemia, prognostic value of, in chronic nephritis, final report; E. Henes, Jr..... 411

Cohn, A. E.: An investigation of size of heart in soldiers by teleroentgen method 119

Colloidal gold reaction and its clinical interpretation; M. Warwick and C. E. Nixon..... 119

Delatour, B. J.: Research on blood sugar in depancreatized dogs..... 405

DeNiord, H. H.: Effect of roentgen rays on metabolism of cancer patients 32

DeNiord, R. N.: Effect of roentgen rays on metabolism of cancer patients 32

Dermographism, sequence and arrangement of pallor and redness in irritated skin of normal and dermographic individuals; L. B. Bibb..... 680

Diabetes, hereditary, case of; F. M. Allen and J. W. Mitchell..... 648

Edema, pulmonary, experimental; B. H. Schlomovitz..... 472

Electrocardiogram, determination of ventricular predominance from electrocardiogram; H. E. B. Pardee..... 683

Electrocardiogram, further observation on T wave of electrocardiogram of dog following ligation of coronary arteries; F. M. Smith..... 673

Electrocardiogram, method of analyzing; H. Mann..... 283

Electrocardiogram, observations on changes in form of initial ventricular complex in isolated derivations of human electrocardiogram; F. A. Willius 550

Elliott, C. A.: Clinical study of yellow fever; observations made in Guayaquil, Ecuador, in 1918.. 174

Exostosis, multiple cartilaginous; four cases with report of calcium and magnesium metabolism in two cases; J. A. Honeij..... 584

Eyster, J. A. E.: Experimental determination of influence of abnormal cardiac rhythms on mechanical efficiency of heart..... 317

Fahr, G.: Analysis of spread of excitation wave in human ventricle..... 146

Foster, G. L.: Studies on arthritis in army based on 400 cases; studies on nitrogen, urea, carbon dioxid combining power, calcium, total fat and cholesterol of fasting blood, renal function, blood sugar and sugar tolerance 243

Gangrene, pulmonary, and fetid spirillar bronchitis; P. Nolf..... 429

Goiter, prevention of simple goiter in man; D. Marine and O. P. Kimball 661

Goldberger, J.: Experimental pellagra in white male convicts..... 451

Graham, E. A.: Sodium carbonate in chloroform poisoning..... 575

Gram, H. C.: On platelet count and bleeding time in diseases of blood.... 325

Heart, analysis of spread of excitation wave in human ventricle; G. Fahr 146

PAGE

Heart, clinical observations on unusual mechanisms of auricular pacemaker; P. D. White..... 420

Heart, experimental determination of influence of abnormal cardiac rhythms on mechanical efficiency of heart; J. A. E. Eyster and E. C. Swarthout 317

Heart, investigation of size of, in soldiers by teleroentgen method; A. E. Cohn..... 499

Heart, teleroentgen estimations of heart size in cases of effort syndrome; B. Smith 532

Hearts, teleroentgen measurements of, of normal soldiers; B. Smith..... 522

Henes, E., Jr.: Prognostic value of cholesterinemia in chronic nephritis 411

Honeij, J. A.: Cavity formation and annular pleural shadows in pulmonary tuberculosis 63

Honeij, J. A.: Study of multiple cartilaginous exostosis; four cases with report of calcium and magnesium metabolism in two cases..... 584

Ivy, A. C.: Physiology of stomach; studies on gastric ulcer..... 6

Jaundice, toxic, in patients under antisyphilitic treatment; study of chemical analyses of blood and urine, and observations on effect of exercise and diet in treatment of syphilis; C. V. Bailey and A. MacKay.. 628

Kahn, M.: Protein and lipin content of blood serum in nephritides..... 112

Kimball, O. P.: Prevention of simple goiter in man..... 661

Liver, effect of acute yellow atrophy on metabolism and on composition of liver; W. O. Stadie and D. D. Van Slyke..... 693

Lung, comparison of various standards for normal vital capacity of lungs; H. F. West..... 306

Lung, edema of, experimental; B. H. Schlomovitz..... 472

Lung, fetid spirillar bronchitis and pulmonary gangrene; P. Nolf..... 429

MacKay, A.: Toxic jaundice in patients under antisyphilitic treatment; study of chemical analyses of blood and urine, and observations on effect of exercise and diet in treatment of syphilis..... 628

Mann, H.: Method of analyzing electrocardiogram..... 283

Marine, D.: Prevention of simple goiter in man..... 661

Meakins, J.: Harmful effects of shallow breathing with special reference to pneumonia 1

Meningitis, purulent typhoid meningitis; report of case; E. A. Baumgartner and H. H. Olsen..... 537

Metabolism, effect of roentgen rays on metabolism of cancer patients; R. N. DeNiord, B. F. Schreiner and H. H. DeNiord..... 32

Mitchell, J. W.: Case of hereditary diabetes..... 648

Moore, J. E.: Cerebrospinal fluid in multiple sclerosis..... 58

Nephritides, protein and lipin content of blood serum in; M. Kahn..... 112

PAGE

Nephritis, prognostic value of cholesterinemia in, final report; E. Henes, Jr. 411

Nervous system, vagus, irritation of vagus and hemorrhagic erosions of stomach; K. Nicolaysen 295

Nicolaysen, K.: Irritation of vagus and hemorrhagic erosions of stomach 295

Nixon, C. E.: Study of colloidal gold reaction and its clinical interpretation 119

Nolf, P.: Fetid spirillar bronchitis and pulmonary gangrene 429

Olsen, H. H.: Purulent typhoid meningitis 537

Pardee, H. E. B.: Determination of ventricular predominance from electrocardiogram 683

Pellagra, experimental, in white male convicts; J. Goldberger and G. A. Wheeler 451

Pemberton, R.: Studies on arthritis in army based on 400 cases; studies in relation of creatin metabolism to arthritis 335

Pemberton, R.: Studies on arthritis in army based on 400 cases; observations on basal metabolism 241

Pemberton, R.: Studies on arthritis in army, based on 400 cases; preamble and statistical analysis 231

Pemberton, R.: Studies on arthritis in army based on 400 cases; roentgen-ray evidences, clinical considerations, treatment, summary, conclusions and clinical abstracts of cases studied 351

Pemberton, R.: Studies on arthritis in army based on 400 cases; studies on nitrogen, urea, carbon dioxid combining power, calcium, total fat and cholesterol of fasting blood, renal function, blood sugar and sugar tolerance 243

Pericarditis with effusion, an experimental study; C. S. Williamson 206

Pneumonia, harmful effects of shallow breathing with special reference to pneumonia; J. Meakins 1

Rat bite fever, report of case; A. Arkin 94

Respiration, clinical studies on respiration; comparison of various standards for normal vital capacity of lungs; H. F. West 306

Robertson, J. W.: Studies on arthritis in army, based on 400 cases; preamble and statistical analysis 231

Roentgen rays, effect of, on metabolism of cancer patients; R. N. DeNiord, B. F. Schreiner and H. H. DeNiord 32

Roentgen ray, influence of exposure to roentgen ray on progress of tuberculosis; J. A. Weinberg 565

Schlomovitz, B. H.: Experimental pulmonary edema 472

Schreiner, B. F.: Effects of roentgen rays on metabolism of cancer patients 32

Sclerosis, multiple, cerebrospinal fluid in; J. E. Moore 58

Skin, sequence and arrangement of pallor and redness in irritated skin of normal and dermographic individuals; L. B. Bibb 680

PAGE

Smith, B.: Teleroentgen estimations of heart size in cases of effort syndrome 532

Smith, B.: Teleroentgen measurements of hearts of normal soldiers..... 522

Smith, F. M.: Further observation on T wave of electrocardiogram of dog following ligation of coronary arteries..... 673

Sodium carbonate in chloroform poisoning; E. A. Graham..... 575

Stadie, W. C.: Effect of acute yellow atrophy on metabolism and on composition of liver..... 693

Stomach, irritation of vagus and hemorrhagic erosions of stomach; K. Nicolaysen 295

Stomach, physiology of; studies on gastric ulcer; A. C. Ivy..... 6

Stomach ulcer, studies on; A. C. Ivy..... 6

Sugar in blood in depancreatized dogs; B. J. Delatour..... 405

Swarthout, E. C.: Experimental determination of influence of abnormal cardiac rhythms on mechanical efficiency of heart..... 317

Syphilis, toxic jaundice in patients under antisyphilitic treatment; study of chemical analyses of blood and urine, and observations on effect of exercise and diet in treatment of syphilis; C. V. Bailey and A. MacKay 628

Teleroentgen estimations of heart size in cases of effort syndrome; B. Smith 532

Teleroentgen, investigation of size of heart in soldiers by teleroentgen method; A. E. Cohn..... 499

Teleroentgen measurements of hearts of normal soldiers; B. Smith..... 522

Tompkins, E. H.: Studies on arthritis in army based on 400 cases; observations on basal metabolism..... 241

Tuberculosis, cavity formation and annular pleural shadows in pulmonary tuberculosis; J. A. Honeij..... 63

Tuberculosis, influence of exposure to roentgen ray on progress of tuberculosis; J. A. Weinberg..... 565

Typhoid, purulent typhoid meningitis, report of case; E. A. Baumgartner and H. H. Olsen..... 537

Vagus, irritation of vagus and hemorrhagic erosions of stomach; K. Nicolaysen 295

Van Slyke, D. D.: Effect of acute yellow atrophy on metabolism and on composition of liver..... 693

Warwick, M.: Study of colloidal gold reaction and its clinical interpretation 119

Weinberg, J. A.: Influence of exposure to roentgen ray on progress of tuberculosis 565

West, H. F.: Clinical studies on respiration; comparison of various standards for normal vital capacity of lungs..... 306

Wheeler, G. A.: Experimental pellagra in white male convicts..... 451

White, P. D.: Clinical observations on unusual mechanisms of auricular pacemaker 420

PAGE

Williamson, C. S.: Pericarditis with effusion..... 206

Willius, F. A.: Observations on changes in form of initial ventricular complex in isolated derivations of human electrocardiogram..... 550

Yellow atrophy, acute, effect of, on metabolism and on composition of liver; W. C. Stadie and D. D. Van Slyke..... 693

Yellow fever, clinical study of; observations made in Guayaquil, Ecuador, in 1918; C. A. Elliott..... 174

Fifty cents each will be paid for the following issues of the Archives of Internal Medicine: January, March, June, August, 1918. January and July, 1916; November, 1915; January, 1911; July, 1909. AMERICAN MEDICAL ASSOCIATION, 535 North Dearborn Street, Chicago, Ill.

A Timely Therapeutic Reminder—

CINCHOPHEN CALCO

Increased incidence of Rheumatism in the Spring and early Summer offers further opportunities for utilizing the pronounced analgesic action of CINCHOPHEN CALCO.

Its freedom from untoward effects upon heart and kidneys is particularly appreciated in rheumatism, since here cardio-renal impairment so frequently already exists or its development is feared.

CINCHOPHEN CALCO has become one of the standard remedies in medicine. Physicians are urged to specify CINCHOPHEN CALCO. It is a quality guarantee, a prerequisite for therapeutic efficacy.

Detailed literature on request

Calco

Manufactured by

THE CALCO CHEMICAL COMPANY

Pharmaceutical Division 136 Liberty St., NEW YORK

NOTE:—CALCO THERAPEUTIC AGENTS are, in their fields, recognized standards. A complete list with brief descriptive notes will be gladly supplied on request.

LISTERS
PREPARED CASEIN
DIABETIC
Flour

ANALYSIS

MOISTURE	10.66
ASH	1.63
FAT	0.67
PROTEIN	69.95
STARCH	0.00
SUGAR	0.00
LEAVENING AND FLAVORING	17.09

Makes *strictly*

Non-Carbohydrate BREAD

and other palatable foods

Sent direct—month's supply, $4.85

LISTER BROS., INC.

405 Lexington Avenue NEW YORK CITY

LAWS AND BOARD RULINGS

Regulating the Practice of Medicine in the United States and Elsewhere

A convenient hand book giving for each state and territory practically every essential feature in its medical laws and regulations. It covers the subjects of regulation of medical practice, requirements for licensing, conditions for granting reciprocity, names and addresses of licensing board members, examination dates. Included also is a list of medical colleges with complete data as to entrance requirements, A. M. A. classification, standing in the various states, etc. In a separate section is a list of foreign medical colleges and brief statements concerning requirements to practice in foreign countries.

227 pages. Stiff paper cover. Price, 50 cents.

AMERICAN MEDICAL ASSOCIATION, 535 North Dearborn Street, Chicago

FOR **DIABETICS**

CELLU FLOUR

A non-nutritive flour for filling out reduced diets

27 oz. Bags $2.50 postpaid

Larger quantities at lower rates—Recipes furnished

DIETETIC CELLULOSE COMPANY

2557 W. Chicago Ave. CHICAGO, ILL.

SYPHILIS AS A MODERN PROBLEM

By

William Allen Pusey, M. D.

THIS work is a substantial presentation of the subject of syphilis considered from the standpoint of the disease as it affects the individual and society. Written with the view of interesting particularly the intelligent layman, it is sufficiently detailed and complete to be of interest and value to the physician. This is a book that you will enjoy reading yourself and one that you will wish to recommend to friends interested in sociological problems.

The following chapter headings will give an idea of the originality and scope of the volume:

The beginning of Syphilis
The History of Syphilis to the end of the Nineteenth Century
The History of Syphilis in the Twentieth Century
The Course of Syphilis. The Incubation Period and the Primary Stage
The Course of Syphilis (Continued). The Secondary Stage
The Course of Syphilis (Continued). Tertiary Syphilis
Hereditary Syphilis
The Pathology of Syphilis
The Prognosis of Syphilis
Syphilis and Marriage
The Etiology of Syphilis
The Prophylaxis of Syphilis

129 Pages. Green Cloth Binding, Price 75 Cents, Postpaid.

SUGGESTIONS TO MEDICAL AUTHORS

Including

Style Book of the A. M. A. Press and Guide to Bibliographic References

The medical writer will find in this little pamphlet just that information which he needs when preparing copy for publication. Strict adherence to the rules herein laid down will result in presentable manuscript with properly arranged bibliography and footnotes and correct punctuation. The style book answers many of the nice questions of typography and usage which invariably arise in the editing of copy.

Paper cover, 67 pages. Price, 25 cents

AMERICAN MEDICAL ASSOCIATION, 535 N. Dearborn St., Chicago

THE ARCHIVES OF INTERNAL MEDICINE is published by the American Medical Association for the advancement of scientific medicine in the United States and as a medium of publication for research and observation in the domain of internal medicine.

Manuscripts for publication, books for review, and correspondence relating to the editorial management should be sent to Dr. Joseph L. Miller, 122 South Michigan Boulevard, Chicago, or to any other member of the Editorial Board. Communications regarding subscriptions, reprints, etc., should be addressed, ARCHIVES OF INTERNAL MEDICINE, American Medical Association, 535 North Dearborn Street, Chicago.

Articles are accepted for publication on condition that they are contributed solely to the ARCHIVES OF INTERNAL MEDICINE. Manuscripts must be typewritten, preferably double spaced, and the original copy submitted. Zinc etchings, halftones and blocks for colored reproduction of illustrations will be supplied by the publisher when the original illustrations warrant.

Footnotes and bibliographies should conform to the style of the Quarterly Cumulative Index published by the American Medical Association. This requires, in the order given: name of author, title of article, name of periodical, with volume, page, month—day of month if weekly—and year. On receipt of stamped addressed envelope, "Bibliographic Style," containing rules for footnotes and bibliographies, and a list of leading medical periodicals of the world, with approved abbreviations, will be sent. "Suggestions to Medical Authors," a comprehensive pamphlet on the preparation of medical manuscripts, which also includes "Bibliographic Style," will be sent on receipt of twenty-five cents.

Matter appearing in the ARCHIVES OF INTERNAL MEDICINE is covered by copyright, but as a general thing, no objection will be made to its reproduction in reputable medical journals, if proper credit is given.

Authors will receive one hundred reprints free; additional reprints may be obtained at cost.

The domestic subscription price per year of two volumes is $5.00; Canadian rate, $5.25; foreign rate, $5.40 (23 shillings, 28 francs), including postage. Single copies, 50 cents, postpaid.

Make checks, etc., payable to the AMERICAN MEDICAL ASSOCIATION.

OTHER PERIODICAL PUBLICATIONS
of the American Medical Association

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION—Weekly. Covers all the medical sciences and matters of general medical interest. Illustrated. $5 per annum. Single copies, 15 cents.

AMERICAN JOURNAL OF DISEASES OF CHILDREN—Monthly. Presents pediatrics as a medical science and as a social problem. It includes carefully prepared collective abstracts based on recent pediatric literature. Illustrated. $4 yearly. Single copies, 40 cents.

ARCHIVES OF NEUROLOGY AND PSYCHIATRY—Monthly. A medium for the presentation of original articles on nervous and mental diseases, with abstracts from foreign and domestic literature; book reviews, society transactions, etc. Illustrated. $5.00 per annum (after June 30, $6.00). Single copies, 50 cents.

ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Publishes original contributions and full abstracts of the literature on these two subjects, transactions of the important dermatological societies, etc. $5 per annum (after June 30, $6). Single copies, 50 cents.

QUARTERLY CUMULATIVE INDEX TO CURRENT MEDICAL LITERATURE—Quarterly. A complete subject and author index to the worthwhile current medical literature of the world. Issued four times a year. Fourth volume bound for permanent reference. Subscription price, $5 per current year.

For Clubbing Arrangements Address

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn St. CHICAGO

CONTENTS

PAGE

Sodium Carbonate in Chloroform Poisoning. Evarts A. Graham, M.D., St. Louis 575

A Study of Multiple Cartilaginous Exostosis. Four Cases with Report of Calcium and Magnesium Metabolism in Two Cases. James A. Honeij, M.D., New Haven, Conn. 584

Toxic Jaundice in Patients Under Antisyphilitic Treatment. A Study of the Chemical Analyses of the Blood and Urine, and Observations on the Effect of Exercise and Diet in the Treatment of Syphilis. Cameron V. Bailey, M.D., and Angus MacKey, M.B., Woodstock, Ontario, Canada 628

A Case of Hereditary Diabetes. Frederick M. Allen, M.D., and J. W. Mitchell, M.D., Lakewood, N. J. 648

Prevention of Simple Goiter in Man. Fourth Paper. David Marine and O. P. Kimball, Cleveland 661

Further Observations on the T Wave of the Electrocardiogram of the Dog Following the Ligation of the Coronary Arteries. Fred M. Smith, M.D., Chicago 673

Sequence and Arrangement of Pallor and Redness in Irritated Skin of Normal and Dermographic Individuals. Lewis B. Bibb, M.D. (Little Rock, Ark.), Fort Logan H. Roots, Ark. 680

The Determination of Ventricular Predominance from the Electrocardiogram. Harold E. B. Pardee, M.D., New York 683

The Effect of Acute Yellow Atrophy on Metabolism and on the Composition of the Liver. William C. Stadie and Donald D. Van Slyke, New York 693